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ALCOHOLISM AND DRUG ADDICTION

EDITORIALS 4

GUEST EDITORIAL *Dr. A. Wikler* 5

ARTICLES

Psychological Factors In Alcoholism And Drug Addiction *P. G. R. Patterson* 6

Neurological Complications Of Chronic Alcoholism *L. Lorenzi* 11

Treatment of Alcoholism *D. A. Legge* 17

Psychedelics And Addiction—LSD And Marijuana *A. Chaiton* 24

The Smoking Habit *L. Lacey* 29

FEATURES

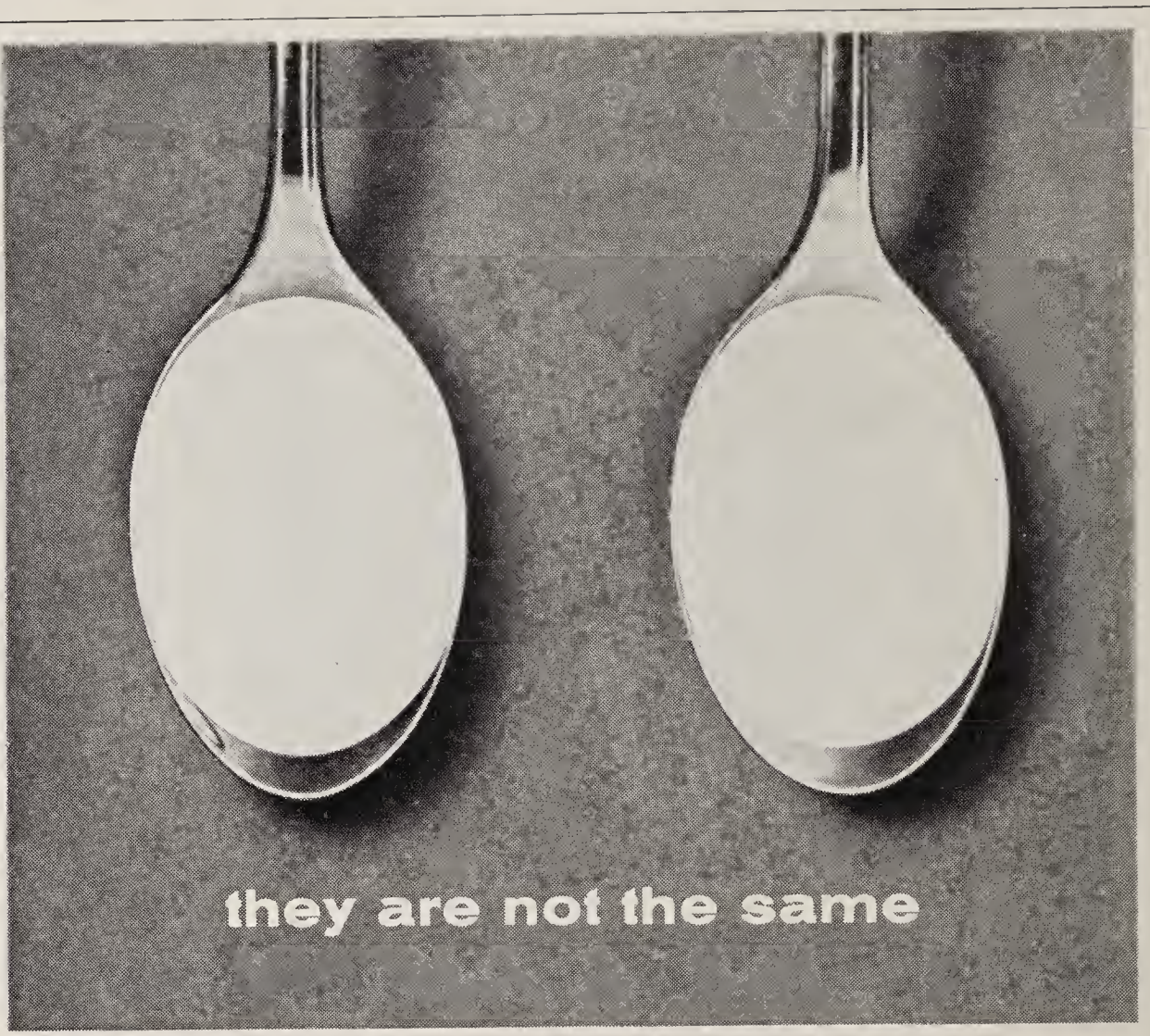
Student Research 21

Special Report 28

Medical Muses 34

Recent Advances 32

Clinicopathological Conference 36



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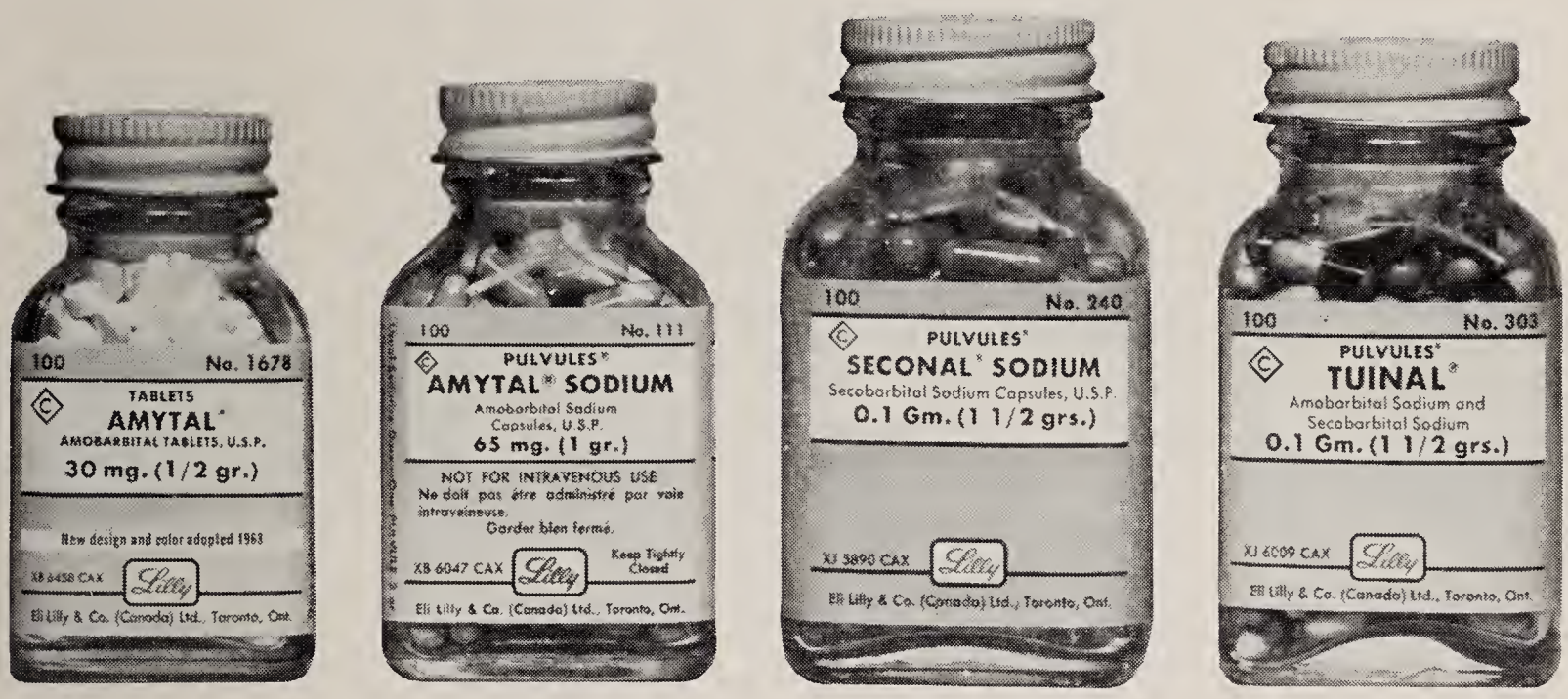

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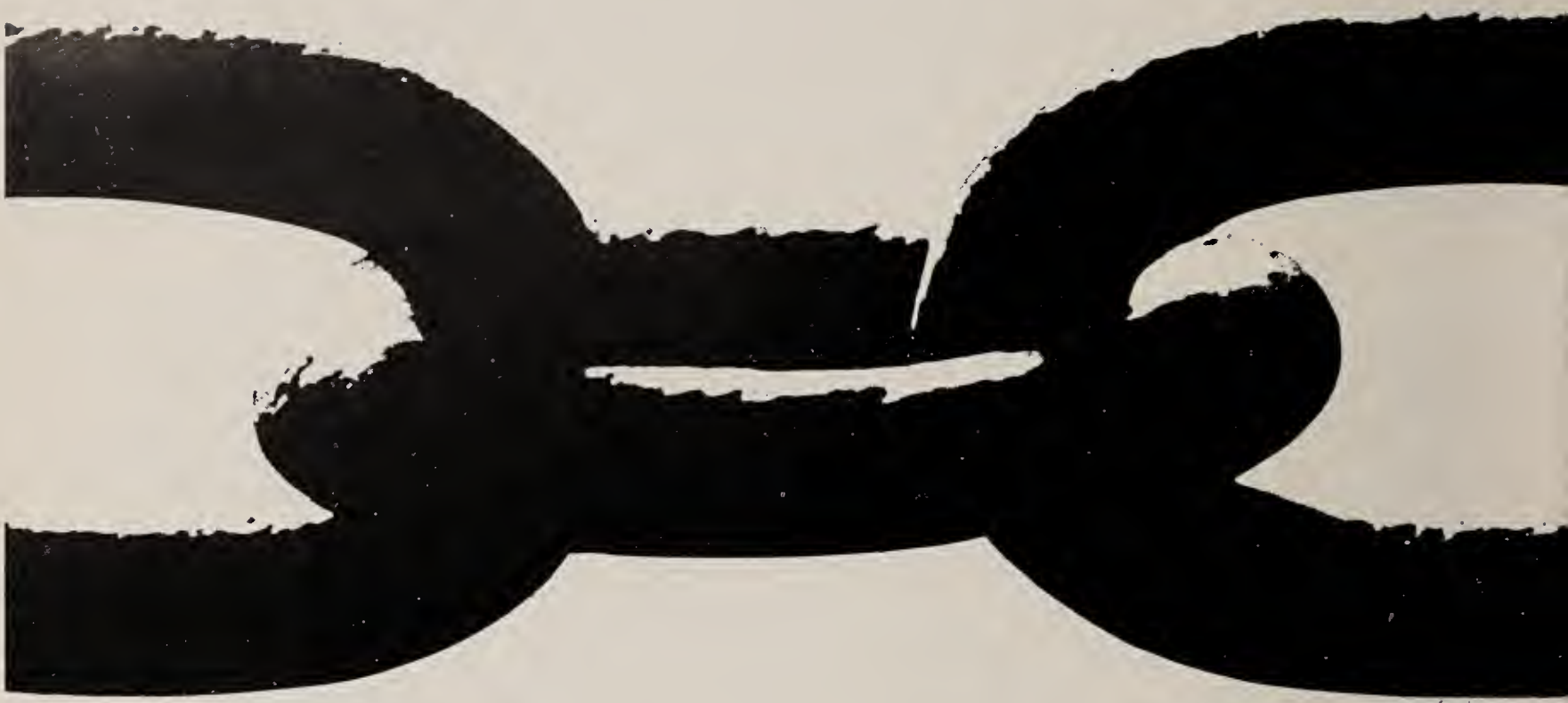

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Editorials

In a general sense, a tendency to addiction or habit formation is one of the most alarming aspects of our twentieth century North American culture. As a people we seem habituated to fast cars, rich foods and the pursuit of individual prosperity. These addictions are, however, accepted by a society which saves its concern for more blatant deviations from the norm. While the medical profession must realize all the consequences of our way of life, we in this issue must be content to pass over man's common failings and deal instead with his abuse of various chemical agents.

This edition has become predominantly concerned with alcoholism more by chance than by design. Despite our original intention to deal equally with the problems of alcoholism and drug addiction, we have found the addictive drugs too varied and the pharmacologic and therapeutic views too copious to allow adequate treatment in an issue of this size. Consequently, we have chosen to deal with the more pressing medical problem, that of alcoholism, disabler of more than five million people in North America alone. Our first three articles centre on the psychological basis for, treatment of, and neuropsychiatric complications of alcoholism and our student research paper presents current thoughts on the pharmacologic actions of alcohol. It is hoped that the information presented may encourage the reader to look beyond the hobnail liver and to think instead of the underlying causes and of the preventive medicine which may be practised in this field. Psychological, sociological and pharmacological treatment may be frustratingly inadequate and difficult to institute, but we are surely duty bound to familiarize ourselves with methods available if we hope to combat this disabling process of staggering proportion.

We have included a paper on psychedelics largely because of the current controversy as to whether these agents are potentially addictive or potentially a threat to mental health as initiators of psychotic reactions. Our further hope with this article is that it may offset some of the misinformation which is available in the popular press, and better enable the reader to propound a rational view of the "heaven or hell drugs" both in medical and non-medical circles.

The concluding paper deals with the smoking habit, our civilization's most intriguing example of voluntary destruction of health. We cannot aim to present new information here but merely to reemphasize the old in the continuing hope that we may succeed in impressing our audience where innumerable authoritative studies have failed with the population at large.

In essence, we hope that this issue may provide some understanding of and compassion for the patient who feels the need for continuous pharmacological support. In the years ahead knowledge will undoubtedly broaden and treatments improve, but in the meantime these articles may help to bridge many of the gaps in our understanding of "addictive disease". S. MacL.

In Volume 44, Clinical Pathological Conferences, introduced and popularly received last year, will be continued. A Student Research feature and a Guest Editorial are two major innovations of this volume. The definitive technical dissertation of a student's research we feel, is best submitted to a specialty journal to be read by specialists. Thus, the object of the Student Research feature is to provide a preliminary report of the student's work, preferably including enough background material to make the research intelligible to a general readership.

Because each issue is centred upon a single theme, we have asked a distinguished authority in each field to write an editorial about his subject. In this issue Dr. Abraham Wikler has graciously provided us with a most lucid first example of this feature. We indeed owe thanks to Dr. Wikler for his valuable time, trouble, and thought. T.W.P. K.P.

Guest Editorial

ABRAHAM WIKLER, A.B. (COLUMBIA);
M.D. (LONG ISLAND COLLEGE OF MEDICINE)

Dr. Wikler is currently Professor of Psychiatry and Pharmacology at the University of Kentucky College of Medicine in Lexington, Kentucky. For twenty years he was on the staff of the National Institutes of Mental Health Addiction Research Center in Lexington. He remains a consultant to this Center. In addition, he is a member of the Expert Advisory Panel on Dependence-Producing Drugs of the World Health Organization in Geneva, Switzerland. He is well-known for his many books and articles on the neurophysiological and pharmacological aspects of addiction.

In an attempt to circumvent the ambiguities with which the terms, "addiction" and "habituation" have become encrusted, the World Health Organization Expert Committee on Dependence-Producing Drugs has proposed[1] the use, in their stead, of the term, "drug dependence," with specification of the type of drug under consideration (morphine type, cocaine type, amphetamine type, cannabis type—presumably also, alcohol type and LSD-25 type). A further distinction is made between "psychic dependence" (common to all types) and "physical dependence" (a potential characteristic of the morphine, barbiturate and alcohol, but not of the cocaine, amphetamine, cannabis or LSD-25 types).

It is important to bear these distinctions in mind, since the medical, psychological and sociological consequences of drug abuse differ in important ways for each type of drug. Nevertheless, certain general principles can be useful in mapping out a strategy of research (and ultimately, of treatment) on so complex a problem. Since "psychic dependence" is common to all types of drug dependence, one needs to inquire into the personalities of habitual users of a drug of a given type, the relevant pharmocological effects of such drugs on their behaviour, the social settings in which such drug use occurs, and the interactions between societal attitudes toward use of a particular drug and the behaviour of the drug user himself. In the cases of drugs that under certain conditions of dosage and frequency of use also produce "physical dependence", additional variables contribute toward the intensification of "psychic dependence"—the development of tolerance and the induction of a synthetic "need" for maintenance of a new level of homeostasis which, if not reduced by continuous administration of the drug, will become manifest in the form of abstinence phenomena (e.g., autonomic disturbances in the case of drugs of the morphine type; convulsions and/or delirium in the cases of drugs of the barbiturate and alcohol types). In these cases, therefore, one needs to inquire also into the chemical-physiological basis of tolerance and "physical dependence," and into conditioning processes resulting from interaction between the environment, the altered state of the organism and drug-acquisitive behaviour. In addition, one needs to inquire into the roles of all of the variables mentioned and possibly others in the genesis of relapse.

Even though the whole of this issue of the Journal is devoted to drug abuse, it is obvious that it can deal only with a few of the variables involved in the problem. Nevertheless, the contents of this issue do exemplify the interdisciplinary approach that must be employed if the problem is to be understood, and eventually solved.

[1]World Health Organization Technical Report Series No. 273. World Health Organization Expert Committee on Addiction-Producing Drugs Thirteenth Report. World Health Organization, Geneva, 1964.

Psychological Factors In Alcoholism And Drug Addiction

Paul G. R. Patterson, B.A. 6T7

I INTRODUCTION

An alcoholic is defined by the World Health Organization as an excessive drinker "whose dependence upon alcohol has attained such a degree that he shows a noticeable mental disturbance or an interference with his bodily and mental health, his interpersonal relations and his smooth social and economic functioning; or shows the prodromal signs of such developments".[1] According to Jellinek[2] "Only when this occurs in conjunction with acquired increased tolerance, withdrawal symptoms, inability to abstain or loss of control may the excessive user of alcohol be termed an alcohol *addict* and his drinking behaviour be regarded as a disease process."

One of the first phenomena discovered by a worker in the area of addiction is that the field fairly bristles with psychological and sociological problems. In fact it would be fair to say that the alcoholic or drug addict without such problems doesn't exist. A certain dilemma, however, arises when one attempts to delineate these problems, weigh them carefully, and place them in their proper perspective with respect to etiology, pathogenesis and therapy. In the first place, Tiebout[4] and Vogel[5] have pointed out that since most alcoholics employ such defense mechanisms as defiance, grandiosity, denial and projection, one has often to be extremely forceful to obtain an admission that *any* problem exists, let alone a psychological one. Secondly, having deduced that a problem exists, one must decide whether it is a present specific adjustment problem in reaction to a certain ongoing life-situation, or whether it is a basic underlying personality problem with roots buried deep in the patient's past. Thirdly, one must make up one's mind as to the relationship of the psychological problems to the physiological ones—the quandary of whether or not the psychological problems pre-dated and were the cause of the physiological addiction or whether they, at least in part, merely resulted from it. Fourthly, one must decide whether or not the psychological problems are of such a nature that they must be tackled before a 'cure' or withdrawal is attempted, whether they can safely be left to deal with after a withdrawal has been effected, or whether they can be ignored entirely and trusted to disappear on their own once the physiological addiction itself has been controlled. And finally, one wants to know whether any generalization at all can be made, or whether each case can only be treated individually on its own merits.

So complex, indeed, does the problem become that one finds oneself constantly trying to sail an even course between the Scylla, on the one hand, of considering the addiction to be merely an ignorable symptom of a basic underlying psychological disease process, and the Charybdis, on the other, of throwing up one's hands in disgust, ignoring the psycho-sociological factors entirely, and dealing with the addiction as merely a mechanical physiological bad habit which has to be broken. The dilemma is made no easier by the well-known difficulty that exists in treating and correcting psychological problems. But in point of fact, neither approach can be considered apart from the other and both aspects have to be dealt with as such. As Wikler and Rasor[6] have pointed out, "It is possible to describe aspects of . . . (addiction) . . . from various social, psychological, physiological and biochemical points of view, and these are all inter-related because, in the last analysis, the phenomena observed involve the integrated organism in its total environment."

It is the point of view of the author that social and psychological aspects of any form of addiction are of paramount importance in etiology and in maintaining the on-going process, and therefore must be considered fully when therapy is undertaken. Much has been written on this topic and further discussion seems redundant. The view of most authors on the subject is neatly summed up by Rasor[7] when he says that "drugs themselves do not make a drug addict any more than alcohol makes an alcoholic" and also that "becoming an addict is a highly individualized process which can be understood only in the context of the individual's personality structure, past life situation, and present interaction with the significant figures of his family and peer group." Ferreting out these psycho-sociological factors, however, is a different matter, for as Zwerling and Rosenbaum[8] have stated with respect to the alcoholic, while a specific character matrix or constellation of personality factors probably exists, it is embedded firmly in a very complex ground of other factors and our present diagnostic categories are unsuited to clarify the matter. In short, they are forced to state that ". . . alcoholism may be found in the setting of any clinical diagnostic state and that specific drinking episodes may occur in relationship to conflicts at *all* personality levels".

Nonetheless it is possible to find certain common characteristics among addicts, both in their backgrounds and in their character structures, and it will be the purpose of the rest of this article to describe some of these and the role they play in the addictive process, together with some of the etiological theories that they have en-

gendered, in the hope that such a description will prove useful to the basic understanding of any whose future work will bring them into contract with this area.

II THE ALCOHOLIC

a) Common Characteristics

Subject to all the limitations outlined in the introduction, and without suggesting that there is such an entity as a 'typical alcoholic character', it may be noted that there are many characteristics common to most alcoholics[5]. As Armstrong[9] so cautiously suggests, "one suspects that certain constellations of personality characteristics may be found more consistently than others in the alcoholic population."

Zwerling and Rosenbaum[8] studied a population of alcoholics and found virtually all categories of neuroses, functional psychoses and character disorders. However, "the significant psychiatric finding was the consistent presence of a number of descriptive-dynamic states which suggested a basic character disorder underlying the varied psychopathologic pictures found in these subjects." They found that 1) the subjects were schizoid—they had a basic sense of isolation and tended to use autistic modes of thought. Even if outwardly they were outgoing and sociable, underneath there was a pervasive emotional detachment and a somewhat paranoid feeling about being constantly an outsider. This feeling was frequently countered by grandiosity, denial and an egocentric conviction of omnipotence. 2) The subjects were depressed. There was a basic underlying sense of inferiority, hopelessness, futility, and sadness — often with a facade of joviality and gaiety—and which was often expressed as boredom, loneliness or moodiness. 3) The subjects were dependent, and immature. They had an irrational reliance on external agents for security and care expressed as an infantile orientation to other persons as the providers of love, food and acceptance and also expressed in their passive role to life as being beyond their powers to cope. Their centres of gravity had shifted from themselves to others. These characteristics were frequently concealed behind a great deal of aggressive activity directed toward immediate gratification. 4) The subjects were hostile. There seemed to be no uniform pattern for dealing with this—some directed it outwardly, as in the 'ugly' alcoholic, whereas others directed it inwardly as in the 'weeping' alcoholic. Most displayed an almost insatiable need for self-punishment. 5) The subjects were sexually immature with a basic sense of failure in masculine identification. This was expressed usually in ill-treatment of, and hostile feelings for, females, but not infrequently as overt homosexuality.

Other features found in alcoholics are 6) unrealistically high levels of aspiration coupled with limited achievements leading to perpetual frustration. 7) Very poor impulse control—stemming partly from a desire for immediate gratification and a poorly developed ego — and leading to a dangerous willingness to take chances, and an impatience and inability to wait. 8) Gliedman has pointed out that the alcoholic has a warped time sense such that he lives only in a constantly expanded present. He is incapable of recalling his past experiences in proper sequence or order to utilize them, and he also has little capacity to envision or plan the future[9]. 9) Above all, and pervading all else, the alcoholic is anxious. This anxiety stems from many sources, some undoubtedly being deep-seated intrapsychic conflicts, with others stemming from later conflicts arising directly from his drinking. The realization of the basic anxiety of the alcoholic is all important, for it is at least partly because alcohol reduces this that he drinks. These characteristics present a rather confusing picture, because many of the underlying tendencies and feelings are dealt with by opposing facades erected by the time-honored defense mechanism of reaction formation. This is the source of the tremendous inconsistency seen in the alcoholic and explains why he is so frustrating to deal with, because often his reaction formations fail and the underlying opposing tendency shows through. Then, no sooner are his defenses down and frank communication seemingly established, than he suddenly re-erects his barriers and reverts to his former attitude of denial and omnipotence. Therefore, it is necessary to look well below the surface to understand an alcoholic and to constantly bear in mind the fact that any alcoholic is seldom what he appears.

To sum up, then, the alcoholic is usually a tense, infantile, immature, depressed and anxiety-ridden individual with deep-seated dependency needs, and feelings of guilt, inadequacy, inferiority, and hostility who, if his defense mechanisms and the alcohol are working properly, frequently presents himself as a strong, independent, cheerful, friendly, easy-going devil-may-care bon vivant with only one trouble—he drinks too much.

b) Psycho-sociological Theories of Etiology

1) non-specificity and learning theories

These are among the more superficial theories, although they are no less useful for that reason. They all start with a 'given' of an individual with some sort of psychological or personality problem and it is because they do not specify this problem that they are labelled 'non-specific'. The rest of the argument is that such a predisposed person, confronted with a difficult life situation, finds that drinking diminishes the anxiety involved and that alcohol may serve as a defense through several mechanisms, i.e. diminished awareness of internal or external stress, or the facilitation of defenses previously inhibited. These theories, unfortunately, do not explain either why alcohol is the chosen anxiety-reducer, nor why all anxious people are not alcoholics. To account for this, theories of a hereditary biological predisposition to alcoholism have therefore been added by some to the learning theory approach[2].

2) SOCIO-CULTURAL THEORIES

These theories, in general, do not attempt to fully explain alcoholism but merely add contributing factors. Socio-cultural groups may be divided into high, medium and low acceptance groups with respect to alcohol. In Ireland, for instance, there is a high acceptance. In such an area we may find the emergence of a fairly easy dependence on alcohol simply through a learned pattern of what is commonly accepted in one's associates, and, indeed, there is a high incidence of alcoholism amongst the Irish. Jellinek[11] has pointed out that in such a population one would need relatively less of a personality problem to lead one into alcoholism than in a low-acceptance group such as among the Jewish people, where drunkeness is severely condemned and alcoholism is at a minimum. Thus one would expect to, and does, find that Jewish alcoholics tend to exhibit a higher proportion of severe personality problems and often a rebelliousness against their own culture. The crucial factor seems to be whether a given attitude towards drinking positively suggests drinking to the individual as a means of relieving his inner tensions or whether such a thought arouses strong counter-anxiety[8].

3) PSYCHOANALYTIC THEORIES

For the most part, the psychoanalytic theories tend to dispense somewhat summarily with the alcoholism itself as being merely a symptom and rather emphasize the psychological development of the alcoholic as being the source of the anxieties that have driven him to take this course. Some are content with merely giving the reasons for the basic underlying characteristics of the alcoholic described earlier, whereas others, notably Levy[12], go further to try to explain why alcohol itself was chosen as the instrument to try to alleviate the problems.

Robert Knight's[13] description is the most classic. Due to an over-protective and indulgent mother who used many sources of oral gratification to pacify her child, or to a cold rejecting mother who used no oral gratification, the ego development of the child tends to be arrested at the oral stage. His personality is thus characterized by excessive demands for indulgence which are doomed to frustration in the adult world and this leads to an intolerable disappointment and rage. His resultant hostile acts and wishes against the thrwarting individuals are both socially and personally unacceptable, and he thus feels guilty and punishes himself masochistically. As reassurance for these guilt feelings and for fear of his own masochistic tendencies, he has an excessive need for affection and indulgence, and since this can't be fulfilled the result is more frustration. For such an individual, alcohol is a) a pacifier for disappointment and rage and is a potent means of carrying out hostile impulses to spite his parents and friends, b) is useful for masochistic debasement and c) is a symbolic oral gratification of the need for affection.

Lolli, for many complex reasons, considers alcohol to be a 'mother's milk' substitute. Brill considers alcoholism as a flight from homosexual impulses, incestuous thoughts and masturbatory guilt. Rado suggests that alcoholism is mainly a problem of depression, the alcohol producing pharmacologically a magical sense of elation which the patient craves[10]. Rado[14], and Tiebout[15] as well, point out the ease with which alcohol permits the fulfillment of the megalomanic drives of 'His Majesty the Baby', characteristics of whom, such as omnipotence and inability to withstand frustration, are perpetuated in the older alcoholic. Menninger emphasizes the self-destructive drives of the alcoholic and terms alcoholism 'chronic suicide'.[10] Levy[12] lists eight dynamic functions of the specific chemical 'ethyl alcohol' including the discharge function, the narcotizing function, the "infantomimetic' function, and the masochistic function and demonstrates the need for these in most alcoholics.

In summary of the etiological factors in alcoholism one cannot do better than to quote Zwerling and Rosenbaum[8]: "In essence the alcoholic is seen as having been rendered vulnerable, by early security-threatening experiences of deprivation, to addiction to a magical fluid which dispels tension and depression, relieves the sense of aloneness, places an instantaneously available source of pleasure at his disposal, permits the mastery and simultaneously the expression of unmanageable and hostile feelings and has a virtually built-in and guaranteed array of sufferings and punishments which serve both to appease the conscience mechanism and to feed back stress stimuli for continuing the cyclic addictive process."

III DRUG ADDICTION

a) BARBITURATE ADDICTION

Nearly all authors are agreed that the barbiturate addict differs very little from the alcoholic in most respects, and that they are very often the same person. This is because the pharmaco-dynamic effect of barbiturates differs hardly at all from that of alcohol. Both impair the sensorium and the mentality. According to Peterson[17]: "In contrast to the social and sexual passivity and relative alertness of the satisfied dope addict, the barbiturates user will be confused, ataxic, and sometimes outright belligerent. His mood shows frequent changes. He will be unable to complete simple motor tasks. His sexual excitement and performance may be increased as well as his appetite for food." Thus the barbiturates user will not be considered separately from the alcoholic.

b) NARCOTICS ADDICTION

Much of what has been said about the alcoholic is also true of the narcotics addict, and the emphasis in this section will accordingly be placed on the points where the two differ.

i) *Differences in pharmacodynamic effects between alcohol and narcotics*

Much has been written about the differences between the effects of alcohol and narcotics, and from these the conclusion has been drawn that there are different forces in operation which draw a potential addict to narcotics rather than to alcohol as a solution to his problems. To quote Nyswander[16]: "Whereas the dynamics of addiction formerly grouped narcotic addiction with alcoholism, pharmacological and psychological data available warrant a clear distinction between the two."

The basic difference between the two types of drug is that alcohol releases inhibitions and permits appetites to be aggressively satisfied, whereas narcotics induce the satiated state themselves and reduce aggression to nil. Narcotics satisfy the basic hunger for food, sex, warmth and love and remove anxiety, pain, frustration, hostility, guilt depression and the need for aggression. Thus a narcotics addict can say, as quoted by Wikler and Rasor[6]: "Drugs make me satisfied; alcohol makes me want to go out and get satisfied."

Another basic difference is that whereas alcohol leads to physical, moral, mental, and personal deterioration and eventually incapacitates the user, with narcotics, anti-social behaviour seldom appears, (where drugs are cheaply available), personal hygiene is kept up, responsibilities are discharged satisfactorily, and psychological tests reveal a clear sensorium with no impairment even after years of use. Thus alcohol is a more self-destructive agent for the addict than narcotics.

The final basic difference between the two forms of drug is the speed with which physiological addiction develops, narcotics being much faster than alcohol.

It is on these variations that the basic personality and etiological differences between alcoholics and narcotic addicts are based.

ii) *Common characteristics*

Like the alcoholic, the narcotics addict tends to be immature, infantile, neurotic, dependent, has a tendency towards omnipotence, grandioisity and magical thinking, and is cursed with an overwhelming all-pervading anxiety. He tends to be even more egocentric than most alcoholics, his sexual identification problems are greater (often having very reduced libido) and he has the same feelings of inferiority and personal inadequacy.

Unlike the alcoholic, though, the narcotics addict tends to have a very flattened affect . . . to be "cool". Because he has little feeling for others in his life there is a very basic disturbance in his interpersonal relationships. Further, he tends to be much more passive than the alcoholic, and will go to great lengths to avoid aggression and recognizes none in himself. He wants to undergo a cool, passive, inconspicuous withdrawal from life. To quote Nyswander[16]: "In his innermost self his idealized image is to be a person who is quiet, untroubled and contemplative." Hence we must conclude that the more generalized incidence of criminality in the drug addict, and his social deterioration is almost entirely due to the great cost of his supply (up to $400.00 a day) which forces him to "pilfer, pimp, prostitute or peddle."

Usually the family background of the narcotics addict is worse than that of the alcoholic. He frequently has had an inconsistent loving-hating mother and a very weak and indifferent father, and he is very poorly identified with the latter (hence his sexual problems). He is much more likely to have come from a slum background in a large urban community.

In summary then, the narcotics addict tends to be more severely disturbed than the alcoholic, to be more immature, infantile and narcissistic, to be more demanding of immediate gratification without the need for making any return, to have more disturbed sexual and other types of interpersonal relationships, and to be much more passive and overtly schizoid. Finally, he tends to use the reaction formation defense mechanism to a much lesser extent, preferring to retreat into his own private chemically-induced world, rather than to aggressively 'bluff it out'.

iii) *Etiology*

Most of the etiological theories of drug addiction are similar to those for the alcoholic, and an extensive review is not necessary here. While the "non-specific and learning theories" are very similar in principle, much more emphasis tends to be placed on the specific qualities and potentials of the drug itself to fulfil the specific psychological needs of the addict—especially the need for passive satiation. Rado[14] quotes an addict as saying: "It (heroin) puts an end to my despair; it makes me feel happy; it restores my self-confidence; and it does all this in a moment, without any effort on my part. The drug is a miracle. I cannot live without it."—rather like an addict's version of the Twenty-Third Psalm!

The psychoanalytic formulation of narcotics addiction is again very similar to that for alcoholism with a few significant differences. The very strong inconsistent mother tends to lead to an earlier, more oral, more narcissistic ego fixation than for the alcoholic, and the inconsistency of her affection probably leads to a stronger distrust of other people as a source of emotional gratification, throwing the addict back more on his own narcissistic resources. Hence, he has more disturbed inter-personal relations. The weak, indifferent father causes poor identification and hence more sexual problems. From this point, Wikler and Rasor[6] outline much the same sequence of steps for the narcotic addict as Knight[13] outlined for the alcoholic. Again, however, more emphasis is placed on the specific abilities of narcotics to fulfil the addict's needs. Rasor[7] points out that the narcotics addict uses the drug to satiate his normal

appetites, and since he has poor love relationships anyway, he finds little loss in his resultant castigation by family and society.

Rado[14] points out that while the mature man is willing to accept a delayed reward, the immature narcotics addict is more insistent upon immediate gratification. Narcotics are admirably suited to give him the biochemical short-circuit he requires. Nyswander[16] suggests that the fact that most addicts become addicted in their late teens in a period of stormy sexual and social re-organization, coupled with the fact that both sexual and aggressive drives are reduced by narcotics, might lead one to conclude that there is an urgent need on the part of the addict to avoid these parts of the normal adult life.

In general, it can be concluded (granted equal availability of the drugs) that although the resultant psychological drive for addiction is probably equivalent in the narcotics addict and the alcoholic, the specific personality factors mentioned are probably just different enough to predetermine which of the two forms of solace the potential addict will choose.

IV IMPLICATIONS FOR THERAPY

Two widely divergent approaches may be taken to therapy. One is to ignore the psychological background of the addiction and to treat the problem as simply behavioural and eliminate the use of the addictive chemical—by force if necessary. The other is to ignore the behavioural problem and to treat only the underlying psychological disorder. In neither case is the treatment likely to be effective. The behavioural manifestations of the addiction, if only because of the physiological aspect, have become a problem in their own right, and concentrating solely on the underlying psychological difficulties (as some psychiatrists seem to attempt to do) is ridiculous. On the other hand, it is to be hoped that this article has pointed out the extreme importance of the role that psychological factors play in addiction, and has made quite clear the fact that simple removal of the addictive behaviour pattern will not leave the patient basically much better off than before, and furthermore will leave the road paved for re-addiction, since the underlying cause has not been removed. Obviously, the correct route is to neglect neither approach, but to attempt both.

Three forces are involved in treatment. One is the physiological addiction, one is the psychological addiction and root, and one is the vector of the forces for rehabilitation. The physiological addiction can be resolved by well-established medical methods. The vector of the forces for rehabilitation can be augmented by legal and familial pressures plus the conquering of some of the addict's defense mechanisms outlined above, forcing him to face the issue — to "surrender", as Tiebout[4] puts it. This latter is often an extremely difficult task, but can be accomplished by recognizing the forces which originally invoked the defense mechanisms. And, finally, the psychological addiction must be removed—the most difficult but most necessary task of all. This must be done by first recognizing the underlying needs of the addict, secondly by reducing these needs by psychiatric procedures, and finally by providing a more acceptable method than the addictive chemical for dealing with those needs which cannot be eliminated.

With the adequate recognition of all these factors, both physiological and psychological, it is to be hoped that more success may be met with in treating the problem of addiction. The task is difficult enough itself, without leaving out half of the factors involved as so many are tempted to do . . . a fact that has led to so many frustrations and failures that the doughty old Ben Franklin was once moved to remark that there were many more old drunkards than old doctors!

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Neurological Complications Of Chronic Alcoholism

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CLASSIFICATION (Modified after Harrison)[14]

I ALCOHOLIC INTOXICATION
- a) Simple Drunkenness
- b) Alcoholic Coma
- c) Alcoholic Excitement ("Pathologic Intoxication")

II ABSTINENCE OR WITHDRAWAL SYNDROME
- a) Alcoholic Tremulousness
- b) Alcoholic Hallucinosis
- c) Acute and Chronic Auditory Hallucinosis
- d) Alcoholic Epilepsy
- e) Delirium Tremens

III NUTRITIONAL DISEASES OF NERVOUS SYSTEM
- a) Wernicke-Korsakoff Syndrome
- b) Polyneuropathy (Neuritic Beri Beri)
- c) Alcohol (Nutritional) Amblyopia
- d) Pellagra

IV DISEASES OF UNCERTAIN PATHOGENESIS
- a) Cerebellar Degeneration
- b) Marchiafava-Bignami Disease
- c) Central Pontine Myelinolysis
- d) Cerebral Cortical Atrophy

I ALCOHOLIC INTOXICATION

The various clinical manifestations of alcoholic intoxication are a direct result of the action of alcohol on nervous tissue. Alcohol has an inhibitory action on the CNS due to its interference with the active transport of electrolytes across the cell membrane[1]. In low concentrations alcohol causes a mild depression of the RAS releasing the cerebral cortex from selective inhibitions and control mechanisms; in higher concentrations there is depression of the whole nervous system.

a) Simple Drunkenness

This is the most common manifestation of alcoholism and its clinical features are well known. There is a varying degree of abnormal behaviour, feeling of relaxation or exhilaration, impaired judgment, loss of emotional restraint, slurred speech, irritability, numbing of sensation, drowsiness. No specific treatment is required. Certain time-honoured remedies, such as strong coffee, induced vomiting, alternating warm and cold showers and forced activity, may help, but there is little evidence that they significantly alter the natural short-lived course of this condition.

b) Alcoholic Coma

Alcoholic coma is essentially a deep anaesthesia. As the margin between alcohol-induced surgical anaesthesia and depression of respiration is very narrow, alcoholic narcosis may at times be fatal. Death is usually due to respiratory and/or circulatory failure. Coma persisting for more than twelve hours is likely to be fatal. Children's tolerance for alcohol is disproportionately low and they may be poisoned by alcoholic fumes or small amounts of alcohol may result in severe intoxication. It is of interest that in a child severe intoxication is not usually preceded by drunkenness and coma with or without convulsions commences soon after drinking.

In alcoholic coma, the pupils are very small but when the patient is shaken the pupils dilate and constrict again when the patient is left at rest. This sign (Macewens's) is very characteristic of alcoholic coma. Treatment must be prompt and energetic, but one must be wary of other causes of coma in the alcoholic patient, particularly sub-dural hematoma.

c) Alcoholic Excitement

This well-defined nosological entity occurs in only a small proportion of acutely inebriated patients. It consists of a sudden onset of marked excitement and impulsive, aggressive behaviour, which may progress to destructive actions and/or crimes of violence. A pathognomonic sign is the loss of pupillary reflex with unimpaired speech and motor co-ordination. The patient will eventually become stuporous and in the end retain no memory of the episode.

It appears that this interesting phenomenon is due to an abnormal reaction to alcohol, whereby the reactivity threshold of the brain is lowered so that even small quantities of alcohol will produce abberrations of consciousness.

The original personality structure appears to be blocked and a completely different one emerges. Previous craniocerebral trauma, constitutional differences in susceptibility to alcohol, and an underlying epileptic presdisposition have been implicated in the etiology. However, there is little evidence supporting any of these factors.

Treatment consists of physical restraint and parenteral sedation, e.g. Amytal sodium 7½ grs. (500 mg.) I.M., repeated once in 30 minutes if necessary.

II WITHDRAWAL SYNDROME

A wide variety of symptoms and signs may be induced by the withdrawal of alcohol after prolonged intoxication or after days of particularly heavy drinking. According to an Expert Committee of the World Health Organization[2] "Withdrawal symptoms may be defined as those manifestations which appear either after cessation of drinking or even after an abrupt decrease in the rate of intake, either of which, in the opinion of the Committee, constitutes a "withdrawal". It follows that such symptoms are not present as long as a sufficient degree of intoxication is maintained and that these symptoms can be relieved by alcohol or some drug with similar pharmacological effects (e.g. paraldehyde, barbiturates, and chloral hydrate)".

a) Alcoholic Tremulousness

This is the most common form of the withdrawal syndrome. Characteristically, the patient is alert, anxious, easily startled and has a marked tremor of the extremities. His face is flushed and his conjunctivae are injected. There are associated G-I symptoms, e.g. nausea, vomiting, anorexia. These symptoms can be temporarily relieved by further intake of alcohol only to reappear a few hours later when the patient abstains once again. The patient usually remains well-oriented in all spheres and his memory is intact; generally this symptomatology subsides within a few days. However, some of the instability, agitation, insomnia and tremulousness may persist for a longer period of time.

b) Alcoholic Hallucinosis

Aberrations of perceptual content occur in approximately 25% of the tremulous patients[14]. The hallucinosis frequently occurs in patients who have had several sleepless days and nights and are exhausted. Clinically, the condition is characterized by intense hallucinations, usually visual or auditory in nature, somatic delusions, paranoid ideas, motor unrest and anxiety. There is minimal clouding of the sensorium. There are often delusions of persecution based on the hallucinatory experiences and the patient may try to "escape" by seeking police protection or attempting suicide. At times the clinical picture may be difficult to distinguish from schizophrenia. Bleuler and other authors have actually put forth the theory that this condition "is" a form of schizophrenia[11]. However, actual attempts at linking the two conditions have failed.

In the differential diagnosis, one must consider especially the following: Schizophrenia, Epilepsy, bromide and amphetamine intoxication.

c) Acute and Chronic Auditory Hallucinosis

This condition is characterized by pure auditory hallucinations without clouding of the sensorium or confusion. Typically, the hallucinations are intense and vivid and very often consist of threatening voices arising from the immediate surroundings. Most patients have no insight into the unreality of their hallucinations, and their reactions are appropriate to the hallucinatory content. Generally, this symptomatology subsides in a few days and normal mentation is restored, but one out of every 8 - 9 patients progresses into a chronic hallucinatory state. Repeated attacks of the acute phase of the condition may render the patient prone to the development of the chronic illness. Again, the theory that this disorder is a form of latent schizophrenia "uncovered" by alcohol seems to be untenable.

d) Acoholic Epilepsy

The exact relationship between alcoholism and epilepsy has long been a question of debate. It is, in fact, known that alcohol exacerbates epileptic conditions and it seems that the incidence of alcoholism among epileptics is higher than among the general population. However, over the past 15-20 years, there has been a tendency to look upon alcoholic convulsions rather as a manifestation of the abstinence syndrome than as epilepsy induced by alcohol. The seizures are always grand mal in type and may occur singly or in succession; rarely they may progress to status epilepticus. During the seizure, there are often EEG abnormalities which, however, disappear shortly after the cessation of the attack. In the intervals between drinking bouts, the EEG remains normal.

In certain patients, the ingestion of excessive quantities of alcohol results in a special type of epilepsy—temporal or psychomotor epilepsy. It consists of the following three cardinal manifestations;

—amnesia (of the episode)
—psychotic equivalents
—destructive or bizarre motor activity

This condition is important from a medico-legal point of view, as the bizarre behaviour may at times result in criminal acts. As an aid in "uncovering" any latent psychomotor seizures which are specifically induced by alcohol, Marinacci[3] has recommended the use of the "alcohol activation EEG".

e) Delirium Tremens (D.T.)

This disorder, also known as the "Saunders-Sutton Syndrome" is the most dramatic and serious complication of alcoholism. Typically the patient has been a heavy drinker for many years (at least five, and more frequently twenty years or more) and the delirium is preceded by an excessive daily consumption of alcohol over 3-4 weeks. The onset is abrupt and is often preceded by poor sleep. In 20% of cases it commences with seizures. It is generally agreed that the following four signs are necessary to establish the diagnosis:

1. hallucinations or mental confusion
2. hyperkinesis
3. wakefulness
4. tremors

The delirium often ends with a deep sleep; when the patient wakens, he is generally lucid, exhausted, hungry and has little memory of his previous delirious state. On the basis of the duration of the acute attack, B. J. Cutshall[4] has distinguished three "grades" of severity in a study of 205 patients:

Grade I: acute attack—less than 24 hrs. 24%

Grade II: acute attack: 24 - 72 hrs. 51%

Grade III: acute attack: more than 72 hrs. 25%

In most recent studies, the overall mortality rates are less than 10%. The usual modes of death are the following:

1. serious complicating diseases (commonly lung and liver disease).
2. Hyperthermia, eventually leading to a state of coma and vascular collapse.
3. no obvious cause.

Laboratory investigation usually reveals an increase in SGOT, SGPT, and a strongly positive urobilinuria, all indicative of acute liver damage. If the serum bilirubin is greatly elevated and clinical jaundice is present, the prognosis must be guarded, as the patient may subsequently die in hepatic coma, if he survives the acute attack. Blood sugar level is at times elevated and serum K^+ is very frequently low, both findings being explainable on the basis of "stress" placed on the adrenal glands. Of particular interest is the fairly constant finding of a low blood magnesium level. Since Mg^{++} deficiency from whatever cause gives a clinical picture which is very similar to the clinical picture in D.T., Mg^{++} depletion has been implicated as one of the pathogenetic factors in D.T. This deficiency has been explained on the following bases:

1. Magnesiuric effect of alcohol
2. Decreased intake of Mg^{++} in the diet
3. Liver dysfunction
4. Increased loss of Mg^{++} in the sweat
5. Stress-conditioned hormonal mechanism.

The etiology of this condition has been a question of debate for many years. Jacobson (1898) and Bonhoeffer (1906) stressed the primary etiological role of "precipitating factors", such as acute infections (especially pneumonia), accidents, operations, diet, etc. Liver damage was subsequently considered as causally important. Then D.T. came to be regarded as a manifestation of the "withdrawal" or "abstinence syndrome". Recently, a new interesting theory has been put forth by Lynch, Raphael and Dixon[5]. They demonstrated that there are fat cysts in the livers of choline-deficient rats and alcoholics and showed that these cysts may rupture into bile canaliculi and/or vascular channels with subsequent embolization to lungs and brain. They found fat embolism to the brain to be common in chronic alcoholics, and advanced the hypothesis that this may be a major etiological factor in the acute and chronic alcoholic psychoses, possibly even leading to death.

III NUTRITIONAL DISEASES OF THE NERVOUS SYSTEM

In this group of disorders, the role of alcohol is considered of secondary importance. The nutritional diseases are a direct result of the displacement of essential nutrients in the diet by alcohol. As different parts of the nervous system may be affected simultaneously, giving rise to various manifestations, this deficiency syndrome should really be called "Alcoholic Encephalopolyneuritis".

a) Wernicke-Korsakoff Syndrome

i) Wernicke's Encephalopathy

Carl Wernicke first described this illness in 1881 and called it "Acute Superior Hemorrhagic Polioencephalitis". It is characterized by the following three cardinal signs:

1) Organic brain syndrome, acute or chronic
2) Ataxia
3) Extra-ocular muscle paresis and/or nystagmus

The mental disturbance usually consists of: indifference, inability to concentrate, lethargy, minimal spontaneous speech, disorientation and confusion and less frequently, delirium, stupor and coma. The ataxia is of varying severity and is infrequently associated with an intention tremor. It is cerebellar in origin and affects predominantly stance and gait. The ocular disorder consists of:

—conjugate gaze paralysis
—mystagmus, horizontal and vertical
—paralysis of external recti muscles

The pathological lesions are found mainly in the brain stem and involve the following areas: thalamus, hypothalamus, mammillary bodies, floor of IV ventricle, peri-aqueductal region, corpora quadrigemina pontine and medullary tegmentum. They consist of varying degrees of necrosis of both neurons and nerve fibers, gliosis, small hemorrhages, proliferative changes in small blood vessels.

Laboratory studies reveal a severe disturbance of carbohydrate intermediary metabolism. Elevations in fasting blood glucose and in blood levels of alpha-ketoglutaric, pyruvic, lactic and citric acid have been repeatedly found and abnormal increases of the latter four constituents have been reported following I.V. administration of glucose. Following the administration of thiamine the fasting blood levels of the various constituents decrease, but reach their lowest levels only after several weeks. Pyruvic acid blood level seems to be the most consistently affected. The biochemical defect is explained on the basis of impaired oxidation of pyruvic acid. As one recalls, pyruvic acid is formed during the

breakdown of glucose via the Embden-Meyerhoff pathway, and thiamine pyrophosphate is one of the coenzymes in the oxidative decarboxylation of pyruvate. Presumably with thiamine deficiency this process would be impaired. Following administration of thiamine the eye signs and the cerebellar symptoms will rapidly disappear, but an abnormality of retentive memory of the Korsakoff type usually persists.

ii) Korsakoff's Psychosis

This disorder may manifest itself in its "pure" state, or, more commonly, be associated with Wernicke's encephalopathy or with polyneuropathy. Clinically, it is characterized by marked impairment of memory function with or without active confabulation. Typically, the patient shows severe memory deficit, especially for recent events, and an inability to establish new memories and to place past events in proper chronological sequence. In the acute phase, one usually finds active confabulation, which, however, is typically absent in the chronic stages of the illness. The clinical picture is usually irreversible, some patients being left with a chronic Korsakoff's, others with varying degree of dementia. The pathological changes in the brain are very similar to those found in Wernicke's. It would then appear from the pathological similarity and the frequent clinical association of Wernicke's and Korsakoff's that these two conditions are two different facets or phases of the same clinical entity.

b) Peripheral Neuropathy

Alcoholic polyneuropathy is usually bilateral, symmetrical and affects chiefly the distal portions of the lower extremities. Onset is gradual and is characterized by pain and decreased sensitivity in the legs, muscular atrophy, which may at times be masked by edema, and changes in skin pigmentation. In more advanced stages, the upper extremities and the cranial nerves (especially the VII) may also be involved. In the severely affected patient, one finds the legs almost paralyzed and the hands useless, the muscles are painful to compression and there are fibrous contractures, which further restrict mobility. One also finds absent deep tendon reflexes and a "glove and stocking" type of hypesthesia and hypalgesia, which may progress to complete anaesthesia. There are essentially no pathognomonic features which can allow one to distinguish this condition from polyneuropathy from other causes. Recovery is usually a slow process even in the mildest cases. Thiamine deficiency is generally considered to be the primary etiological factor here; however, a study by Fennelly et al (1964)[6] indicated that a deficiency of "pantothenic acid", "nicotinic acid" and "pyridoxine" may also be contributory or responsible. Moreover, hypovitaminenia was found to be directly related to previous dietary habits and not to previous alcohol intake.

Histo-pathologic study reveals a progressive breakdown of myelin sheaths and deterioration of axis cylinders in peripheral nerves. In advanced stages, anterior and posterior nerve roots are also involved. From electromyographic studies, it seems that one must distinguish the effects of alcohol itself from the effects produced by avitaminosis. It appears that alcohol per se acts on the distal portions of peripheral nerves of both upper and lower extremities ("alcoholic neuropathy distalis") and causes axon degeneration, while avitaminosis results in generalized demyelinization of peripheral nerves and nerve roots[7].

The treatment of this condition involves bed rest and supportive therapy as indicated. A well-balanced diet with poly-vitamin supplement including high doses of Vit. B_1 (Thiamine) (100-500 mg. daily) is indicated for a prolonged period of time.

c) Alcohol (Nutritional) Amblyopia

This disorder refers to the visual disturbances occurring in nutritional deficiency and which is not due to lesions in parts of the eye concerned with refraction. The onset is insidious, evolving over several days to weeks and there is a progressive blurring of vision. On examination, one finds reduced visual acuity and bilateral, symmetrical, central or centrocecal scotomas. The peripheral fields are intact and temporal pallor may occur in advanced cases.

Pathologic study discloses a bilaterally symmetrical degeneration of the fibers in the optic nerves, chiasm, and tracts corresponding in location to the papillomacular bundles.

Different nutritional factors have been implicated in the etiology of this disorder, viz. Vit B12, Riboflavin and Thiamine. When adequate nutrition is restored or B Vitamins are given in large doses, there is usually a partial or complete recovery, even if alcohol consumption remains excessive. The relationship of "alcohol amblyopia" to "tobacco amblyopia" has been often questioned; it seems, however, that no distinction can be made between the two conditions on pathological and clinical grounds[17]. In tobacco amblyopia, the nutritional deficiency is again of primary importance and a nutritious diet supplemented by large doses of the B Vitamins brings about improvement in vision.

d) Pellagra

Pellagra, or Casal's disease, is due to a deficiency of Niacin and/or of the amino acid Tryptophane, which is the precursor of Niacin in its synthesis by intestinal bacteria. It occurs endemically in areas where maize is the main constituent of the diet. It may also, however, be secondary to other conditions, such as: (1) anatomical and functional alterations in the G-I tract (e.g. gastric cancer, peptic ulcer, malabsorption syndrome, chronic colitis, etc.). (2) conditions with increased need (e.g., pregnancy, lactation, etc.). (3) chronic alcoholism. In the latter group, the deficiency can be explained on the

basis of displacement of essential nutrients in the diet by alcohol, or perhaps on the basis of increased need.

The clinical picture consists of the following features:

1. An acute progressive dermatitis of the exposed areas of the skin.
2. G-I changes — dyspepsia, abdominal pain, vomiting, and typically a persistent diarrhea.
3. Mental changes. In the early phases the mental symptoms are vague and often mistaken for psycho-neurosis. The patient complains of weakness, irritability, fatigue, depression, insomnia, and memory changes. In more advanced stages, neurological signs similar to neuritic beri-beri will become manifest and there will be a progressive deterioration of intellectual functions. In the final stages, true dementia or an actual psychosis will be evident and associated with progressive cachexia and almost uncontrollable diarrhea.

Pathologic study reveals degenerative changes in the cells in the motor cortex, and in the dorsal columns and pyramidal tracts of the spinal cord.

Treatment consists of a nutritious diet, administration of Niacin (50-100 mg. o.d. per os, or parenterally), and commercial preparations of the total Vitamin B complex.

IV DISEASES OF UNCERTAIN PATHOGENESIS

These rare disorders of a diverse nature are usually encountered in alcoholic patients. However, they have also been reported in non-alcoholics. Consequently, the role of alcohol is again probably secondary and the nutritional status in these disorders remains uncertain.

a) Cerebellar Degeneration

This disorder, first described in 1922 by Marie, Foix and Alajouanine, is also known as "Parenchymatus cortical cerebellar atrophy". It is characterized by a gradual onset usually after the age of 40, a slow progression and no significant remissions. The predominant clinical feature is a symmetrical cerebellar ataxia which is more prominent in the lower extremities. Gait is typically reeling and drunken. Infrequent findings are: nystagmus, dysarthria, involuntary movements, optic atrophy and hyperactive or pathological reflexes.

There are no specific abnormal laboratory findings; however, a pneumo-encephalogram will usually reveal a varying degree of dilatation of the fourth ventricle, suggestive of cerebellar atrophy. The pathological lesions are confined to the vermis, especially the anterior and superior parts (including the lingula, central lobule and the culmen). All the neurocellular elements are involved, the Purkinje cells being more severely affected.

Alcohol seems to be of primary importance in the etiology of this disease, even though the precise relationship still remains obscure. The following factors have also been implicated in the etiology: Syphilis, T.B., enteritis, extra-cranial carcinoma, trauma, heat stroke, vitamin deficiency, lead and methyl mercury salts, drug sensitivity, acute rheumatic fever and post-thyroidectomy crisis.

b) Marchiafava-Bignami Syndrome (Degeneration of the Corpus Collosum)

This rare complication of alcoholism has been described mainly in Italian males addicted to red wine. Clinically, one finds varying degrees of psychic and physical abnormalities: excitability, moral and sexual perversion, changes in affect, intellectual deterioration progressing to dementia, epileptiform and apoplectiform attacks, transient hemi-paresis, dysarthria, vertigo, ataxia, and ultimately coma. There is no evidence of increased intra-cranial pressure.

Pathologic study constantly reveals symmetrically located areas of demyelination in the middle layers of the corpus collosum. Axis cylinders are usually better preserved than medullated fibers and there are appropriate reactions in the macrophages and astrocytes. The pathologic picture is unique and allows a diagnosis of chronic intoxication without the availability of any history.

The etiology of this condition still remains essentially obscure. It has been speculated that deficiency of Vit. B1, which has angio-protective properties, may cause lesions in blood vessel walls, which, in turn, would lead to the formation of a serous transudate into the cerebral tissue. However, the condition has never been reproduced experimentally by avitaminosis.

c) Central Pontine Myelinolysis

This rare demyelinating disease was first reported in 1959 by Adams, Victor and Mancall. It is characterized by pathological changes involving the base of the pons. Usually the lesions are midline, symmetrical and approximately equidistant from the floor of the IV ventricle and the ventral pontine surface. They consist of a sharply outlined focus of myelin destruction affecting all fiber tracts. Neurons, axis cylinders, blood vessels and astrocytes are largely unaffected.

Clinically, the disease manifests itself by a rapidly evolving flaccid quadriplegia associated with weakness of the face and tongue, dysphagia and dysarthria. Loss of corneal reflexes, emotional lability and forced crying have also been observed. The course is usually progressive, the patient dying within 2 - 3 weeks after the onset of the illness. The fact that this disorder is strongly, although inconstantly, related to the heavy consumption of alcohol and that it has appeared only in recent years has led some investigators[16] to believe that it is caused by a toxic substance. Exposure to this "toxin", according to this theory, would be predominantly but not exclusively found in alcoholics.

d) Cerebral Cortical Atrophy

It has been found that the brains of chronic alcoholics exhibit convolutional atrophy to a degree which is often beyond that expected for the chronoligic age. These atrophic changes are of varying degrees and tend to be more prominent in the anterior portions of the cerebral hemispheres, but are at times generalized. There are usually associated thickening of the overlying meninges and a symmetrical dilatation of the ventricles. Histopathologic study reveals slight, patchy loss of nerve cells, and glial proliferation. There are often degenerative changes in the cortical neurons, but their significance is uncertain. The clinical correlates are still indefinite. Perhaps, some intellectual deterioration may be attributed to these changes. The etiology of this condition is obscure.

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The Treatment Of Alcoholism

D. A. Legge 6T8

INTRODUCTION

The incidence of alcoholism in modern society is now reaching alarming proportions, and it is thus becoming increasingly important that the physician be capable of dealing with either the overt alcohol addict or, more important, in terms of prevention, of recognizing signs of incipient addiction. The problem too long has been considered moral rather than medical and for this reason there has been a history of reluctance to accept responsibility for treatment. The difficulty is often compounded when the patient himself refuses to consent to treatment, or submits half-heartedly in response to family or other pressures. Nevertheless, the physician must have a thorough knowledge of available treatments for both chronic and acute phases. The latter especially can usually be dealt with satisfactorily by the physician. When further attention is indicated, or when prophylactic measures are warranted, he should know when and where to refer his patient. It goes without saying, that the physician wishing to assume the responsibility of treating a patient, should have sufficient interest and an understanding personality, in order to achieve his objective. Therapy is most often long and arduous, and not without setbacks.

There are many forms of therapy, but the most suitable combination is a matter of personal preference based on the previous experience of the therapist on one hand, and the type of patient on the other. This article will outline the major methods now extant, and should serve to emphasize that treatment is best considered a multidisciplinary approach[1].

ACUTE ALCOHOLIC STATES

Management of the acute stage is almost entirely medical and is, consequently, relatively straight forward; however, care must be exercised since the complications that arise may frequently constitute a threat to life or future well-being of the patient. The acute patient is encountered most often in the out-patient department of a hospital, but the doctor must be capable of handling a case anywhere. Publicly intoxicated persons should always be taken to hospitals or clinics rather than to jails. At present, far too often the drunk is hauled away to jail, and kept temporarily, only to be let out again to resume drinking. Such "revolving door cycle" treatment, usually involving skid-row inhabitants, reflects society's reluctance to confront this essentially medical problem in a mature manner. This traditional backward approach is to be very much abhorred[2].

a) Symptoms of Withdrawal Stage

Symptoms of withdrawal originate primarily in the central nervous and gastro-intestinal systems. Treatment at this time must be aimed at relieiving the headache, profuse sweating, nausea, vomiting, tremulousness, tension, occasional visual or auditory hallucinations and seizures constituting the typical abstinence syndrome.

When visual hallucinations accompanied by marked fear of the objects seen, confusion, and general disorientation are superimposed on the above findings, the condition is labelled "Delirium Tremens." This severe disability develops in five to ten per cent of patients two to four days after commencing withdrawal states. Krystal[4] has suggested any or all of the following as contributing etiological factors in delirium tremens: dehydration, cerebral edema, salt depletion, potassium excess, magnesium depletion, infection, and panic state..

b) Biological Treatment

(i) *General Measures*

These include bed rest, dietary measures, chemotherapy with tranquilizers, anti-depressants and anti-convulsants, and correction of electrolyte deficiencies.

When the patient is first seen in the acute stage, electrolyte determinations are mandatory. Intravenous therapy is usually necessary to correct serious abnormalities. Desoxycorticosterone acetate and ACTH have been widely used in this phase but their mode of action is not readily explained. The patient should be subsequently placed on a high calorie diet rich in protein, carbohydrate and B vitamin supplementation. Tranquillizers are often necessary to combat insomnia and to control restlessness which tends to exhaust both patient and staff and to interfere with intravenous therapy. Diphenylthydantoin (Dilantin) is effective in controlling seizures.

(ii) *Specific Chemotherapy*

There is now a wide range of medications suitable for use in the treatment of both the acute and chronic phases of alcohol addiction. The three major groups of drugs used are the tranquilizers, the anti-depressants and the sedatives. Consideration for use requires a thorough knowledge of the mechanism of action wherever known, paying particular attention to the side effects and untoward reactions of each drug. The patient, in addiction, should always be made aware of these inherent dangers, and be told that the drug is being used only temporarily in his rehabilitation[3].

There are two major groups of tranquilizers. The widely used phenothiazine derivitives include chlorpromazine (Largactil), promazine (Sparine), and trifluoperazine (Stelazine). These help in reducing irritability and restlessness but are rarely essential. Perhaps more effective are the benzodiazepine compounds like chlor-

diazepoxide (Librium), and diazepam (Valium). Librium has anticonvulsant properties and may be an outstanding choice wherever seizures are a complication. With Librium, intravenous fluid replacement may be unnecessary, so that clear fluids may be taken orally from the start. Also an effective, and perhaps more economical than tranquilizers, is a combination of mephenisin, acetylcarbromal, and reserpine. (Anatenson Forte)[5].

Caution must be exercised when using sedatives. Barbituates are not recommended and paraldehyde is contraindicated since it produces, like alcohol, acetaldehyde during metabolism, thus tending to potentiate the effect of alcohol. Chloral hydrate up to 45 gr. per night and glutethimide (Doriden) are sedatives of choice[6]. The latter must be used with care since it too may be addicting. Glatt et al[7] have reported that chlormethiazole (Hemineverin) affected improvement in withdrawal phase treatment in 71 per cent of cases after the third day of trial. This drug has sedative, hypnotic, as well as anticonvulsant properties and has achieved clinical acclaim in Europe.

A once popular measure is the classical "Insulin Cocktail" consisting of 50 c.c. of 50 per cent glucose with 15-50 u. of regular insulin given IV. This treatment has been judged more often on an empirical than on a physiological basis and has generally been replaced as a relaxing and sleep-inducing procedure by the above mentioned agents.

Reliable antidepressants include amitryptyline (Elavil), methylphenidate (Ritalin) and tranylcypromine (Parnate).

c) Psychological and Social Treatment

Treatment of this nature is rarely used in the acute stages, but is more applicable to the chronic patient. However, it goes without saying that understanding and concern for the patient in his often pitiful situation are most desirable in reducing the unpleasantness of treatment.

d) Treatment of Long-Term Complications

Complications are not unexpected, since much time may have elapsed before the patient will submit for treatment. Accordingly, they must be carefully recognized, sought and treated effectively. Hostility on the part of the conscious patient will often enhance the difficulties. In many respects, the alcoholic is the same type of dependent, anxious, hostile, symptom-laden person as the neurotic or hypochondriac[8].

Those complications that require immediate attention include: infections like meningitis or pneumonia, trauma such as head injury, GI manifestations such as hepatic cirrhosis or hemmorhaging eosophagial varices, and damage to central or peripheral nervous system such as brain atrophy and peripheral neuropathy. As in the withdrawal phase, gastritis is particularly common and feeding is a problem. Vitamin B-complex intramuscularly or by mouth is commonly used but is not always necessary. Vitamin B-1 (Thiamine) is most essential because of its role in the Kreb's cycle and known value in reversing the early stages of Korsakoff's psychosis[6].

CHRONIC ALCOHOLISM

The treatment of the established addict can only be undertaken satisfactorily in hospital. The suitable combination of techniques will be determined largely by the make-up of the patient. Some patients are especially amenable to psychotherapeutic methods, while others react more favourably to conditioning techniques like aversion therapy. The ultimate formula for optimum results is a function of the therapist's skill and experience on the one hand, and the patient's willingness on the other.

Most therapeutic measures provide a method of deconditioning the patient by associating the consumption of alcohol with unpleasant consequences; this can be done forcefully, as in aversion therapy, or voluntarily on the part of the patient as he comes to understand the medical consequences of excessive drinking. This understanding can be furthered by the physician in his office where careful explanation and encouragement may contribute to the patient's rehabilitation by helping him to assume the responsible attitude needed for continued treatment. The patient may be told that his disability resembles that of the diabetic. The diabetic acquires a permanent inability to tolerate sugar normally; accordingly he not only has to have medical treatment, but he has to learn to be his own physician, and in many respects, change his way of living. The alcohol addict, he is told, acquires a permanent inability to tolerate alcohol normally; in spite of the number of uses he has had for alcohol. He has to begin to learn how to live in a way that does not involve alcohol or addictive drugs[9]. If the patient can thus accept his inability to drink, a large part of the battle has been won.

The second step in therapy is essentially one of reconditioning. During the stage of heightened suggestibility, when the patient is beginning to accept his weakness, his old patterns of thought may be broken up, and new ones substituted. These should involve an explanation of all aspects of addiction to alcohol; physical, psychological, and social. He should be told that no amount of medication alone will correct the conditions which disturb his alcohol tolerance and that it will not be miraculously repaired by time. The significance of proper nutrition and rest is explained and he should be made to realize that conscious effort will be required during the first two years of abstinence to police his thinking in order to permit new non-drinking habits to develop.[9]

In establishing this psychological build-up, every factor in his personality and situation should be brought to bear and be mobilized. If the patient's attitude can be

moulded as suggested above then the following methods of treatment are more likely to succeed.

a) Pharmacological Treatment

Disulfiram (Antabuse) is commonly used and succeeds because it allows the patient to maintain sobriety long enough for deeper study and therapy to be instituted. It is not, therefore, a cure, and must be taken regularly to be effective. Antabuse works by inhibiting the enzyme responsible for the breakdown of acetaldehyde. Its accumulation causes unpleasant effects in ten to fifteen minutes after taking alcohol. These include vasodilatation, hypotension, and tachycardia often to the point where the patient fears he is about to die. Nausea and vomiting are also common. Numerous side effects have been reported but only acneiform eruptions and halitosis are common.

Patients may commence Antabuse treatments with or without taking a challenge dose to elicit the reaction. The former is usually unnecessary, since the patient willing to take this treatment hears from others or from the doctor about the unpleasant consequences after taking alcohol. Whenever the test dose is given one must be prepared for an overly severe reaction in which case intravenous ascorbic acid should be given, followed by an intravenous antihistaminic, since part of the reaction is due to release of histamine[10].

Antabuse therapy is not recommended for those who lack ability to control sudden impulses e.g. psychopathic patients. However, for those who can resist the impulse the passing of desire brings a great feeling of relief with attendant reinforcement. Consequently Disulfiram is most effective in alcoholics who are strongly desirous of help.

Citrated calcium carbide (Temposil) has recently been used in place of Antabuse. It also inhibits the breakdown of acetaldehyde but the reaction after alcohol is milder. Occasionally it may be too mild to be effective. Whereas Antabuse protects for seven to ten days after taking, the drug Temposil protects for only one day.

b) Psychological Treatment

(i) *Psychotherapy*

The therapist, whether physician or psychiatrist, must seek out the precipitating 'factors' leading to refuge in drinking. Any incidents in the patient's drinking history, over which he feels particularly ashamed, should be analyzed carefully in search of a possible source of motivation for rehabilitation. The aim is, as always, to force the addict into a realization that he is unable to drink in an acceptable manner. Ability to achieve this seems to be proportional to the patient's ego strength[1]. In the alcoholic this is usually low, and must be bolstered by his association with the therapist or with Disulfiram protection, etc. The latter is particularly useful in that it allows needed time for psychological rehabilitation. The alcoholic must learn to understand his motives and drives and be taught how to express them in a less destructive, more mature manner.

In practice these goals are usually difficult to attain, owing either to lack of skill on the part of the therapist, or more commonly, to discouragement or hostility on the part of the patient.

(ii) *Aversion Therapy*

This is similar to treatment with the protective drugs Antabuse or Temposil, in that the idea is brought to bear that the "first drink" will lead to disastrous results, thus establishing a conditioned aversion to alcohol. Dent[11] initiated this method by using apomorphine as the agent inducing the unpleasant consequences of drinking. Apomorphine is injected intramuscularly — IM 1/20 gr., then increased by 3 mg. up to 100 mg. every two to three hours. This is followed by drinking of alcohol in five minutes; vomiting starts in five to ten minutes. Dent in claiming a 70 per cent success rate over one year with this treatment, suggested that the drug acts not so much by setting up a temporary aversion to alcohol as by reducing anxiety and craving, possibly in a manner similar to Antabuse (see above). Oral apomorphine is now used widely in milder cases, treated on an out-patient basis.

(iii) *Group Therapy*

This method is a logical outcome of a lack of personnel available to treat an increasingly large number of patients. It may be excellent for those who communicate well in a group and feel relieved that others share their own problems. A flexible, permissive atmosphere is aimed at, and the therapist should always draw out of the discussion facts about the underlying dynamics of alcohol addiction. From this the patient may be able to derive insight.

(iv) *Psychodrama*

This is the acting out of life situations under the therapist's control in the hope of inducing the patient to release his hitherto unexpressed conflicting ideas and emotions regarding his problem. The technique is still in the experimental stages of development.

c) Social Treatment

(i) *Alcoholics Anonymous*

This agency, reported to have an enormous fund of experience in the field of social rehabilitation, may, except for the completely irreligious or deeply neurotic or psychotic patient, be the mainstay of treatment[1]. Here, the alcoholic meets others who can help provide him with the right psychological environment. He derives comfort and strength from those who like himself have also "gone through the mill." Admission is solely voluntary, requiring only acceptance of the A.A. "Twelve steps and traditions".[12] This organization has claimed that 50 per cent of their members remain abs-

tinent, certainly an encouraging success rate. Now, a separate fellowship, Al-Anon Family Groups[13], consisting of wives, husbands, relatives and friends of problem drinkers, has been established as a valuable adjunct to the rehabilitation available at Alcoholics Anonymous.

(ii) *The Family*

The family often fails to offer adequate support for the alcoholic because its members tend to view his or her behaviour as voluntary rather than as a manifestation of a serious underlying illness. While love still exists between husband and wife, their interpersonal relationships may be used as a source of motivation for rehabilitation of the alcoholic, even to the extent of precipitating a crisis by forced separation[1]. Obviously where no love remains or where both husband and wife are alcoholic the problems are compounded, especially when one's response to the other is unknowingly making the situation worse[14].

d) Recent Therapeutic Adjuncts

As yet mainly experimental these include conditioning by electroshock, LSD-25 treatment, and hypnosis. The last named method has been used with success in Russia. It is probably best in reducing insomnia, or tension states by achieving deep relaxation, and may be successful in conjunction with aversion therapy, e.g. relieving under hypnosis the sensation of nausea associated with drinking bout aftermaths.

PRECAUTIONS

It is essential to set one's therapeutic goal at a practical level. If one shoots too high, one will often fall short. Any combination of techniques may be effective, and the exploitation of anything at all promising should not be excluded simply because it fails to fit one of the purely theoretical preconceptions[14]. Drugs may often be abused because of their easy availability and because they represent an easy solution for the doctor in a hurry. Drugs potentiating the effects of others must be used with caution, and one must be aware of the danger that cross-tolerance will develop to many of the commonly used sedatives and stimulants e.g. barbituates, bromides, amphetamines, resulting in a new addiction even more serious than that to alcohol. The therapist should aim at helping the patient to accept tension, anxiety, and sleeplessness which might be temporarily relieved more easily by a pill. Although psychiatric care beyond the scope of the family physician is often required, the conscientious doctor will remain in touch with the specialist after referral is made and will continue to offer supportive care after intensive psychotherapy is completed.

SUMMARY

The management of the acute phases of alcoholism may often be adequately dealt with by the general practitioner. Usually, however, more satisfactory help, particularly wherever long-term therapy is indicated, is obtained at a hospital or clinic. Nevertheless, the enormity of the problem demands that the physician be capable of recognizing and treating a case wherever and whenever necessary. Once the acute phase has been dealt with, plans for prolonged treatment may proceed. This may take a great deal of time and require a whole battery of workers who must be prepared to accept setbacks. The aim should be not only continued sobriety for the patient, but also better functioning in all areas of life. Ideally, the egocentricity of addiction is replaced by a social sense and an ability to relate, and share with others.

The many techniques currently available have been presented, and hopefully these demonstrate that treatment should be undertaken by understanding people utilizing a multidisciplinary approach.

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INDEX TO ADVERTISERS

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DAFFYDIL '66' 35
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HAMILTON CIVIC HOSPITALS 43
HOMEWOOD SANITARIUM 42
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FAMILY PRACTICE COURSE 43
OSBORNE'S PHARMACY 16
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SMITH, KLINE, and
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Student Research

Biochemical Effects Of Alcohol On Nervous Tissue

I INTRODUCTION

Although the manifestations of alcoholic intoxication and addiction are well-known, the mechanisms by which these effects are produced at the cellular level are still relatively unknown. For the past four years investigations in our laboratory have produced results which have suggested that some of the principal effects of ethanol are due to its interaction with the neuronal membrane resulting in disturbed electrical activity. It is hoped that these findings will contribute to the biochemical explanation of the observed functional disturbances produced by ethanol.

II PHYSIOLOGY

By the use of microelectrodes implanted into various parts of the brains of conscious unanaesthetized rats, it has been found that ascending fibres from the mid-brain are among the first to be affected by progressively increasing concentrations of ethanol. A decrease in the spontaneous electrical activity of this region occurs. Apparently the inhibitory fibers to the cortex are more sensitive to the ethanol because a simultaneous rise in the amplitude of electrical activity of the cerebral cortex is recorded and the threshold stimulation necessary for initiation of seizure discharge is lowered[1]. At higher doses there is progressive depression of all areas of the brain and death eventually results from depression of the medullary respiratory centre.

Electrical activity of nerve cells is generally agreed to be due to the concentration gradients of Na^+ and K^+ and the flow of these ions across the cell membrane[2]. In the resting state, the membrane may be regarded as being relatively permeable to K^+ and relatively impermeable to Na^+ and to anions. Therefore there is a constant efflux of K^+ from the cell unaccompanied by anions with the result that a potential difference is established across the cell membrane with the inside being negative. In the absence of active transport this efflux of K^+ will continue until the concentration gradient is lowered and an equilibrium point is reached where the tendency for efflux down the concentration gradient is just balanced by electrostatic attraction for K^+ resulting from the slight negative potential inside the cell. At this point no further net movement takes place. However, an active transport mechanism does exist. K^+ is pumped back into the cell and the intracellular K^+ concentration is higher than it would otherwise be at the equilibrium point. Because the magnitude of the resting potential is proportional to the ratio $\frac{\text{extracellular } K^+}{\text{intracellular } K^+}$; (according to the Nernst Equation[3]) the active transport maintains a more negative resting potential.

The cell can be stimulated electrically on the conducting portion of the axon, and by acetylcholine (or other neural transmitters depending on the particular cell) on the post-synaptic membrane. Excitation causes a flow of Na^+ into the cell and lowers the negativity of the membrane potential. Once the critical potential for depolarization is reached an action potential is generated and propagated down the axon. The action potential is characterized by a large increase in membrane permeability to Na^+ such that its inflow into the cell transiently reverses the sign of the membrane potential. The height and rate of rise of the action potential therefore depends on the concentration gradient of Na^+ and its rate of flow across the membrane. Subsequently, a delayed increase in K^+ outflow occurs, and balances the Na^+ accumulation. This causes repolarization of the membrane to the normal resting potential.

Therefore with every action potential the cell loses K^+ and gains Na^+. These cations are subsequently restored to their appropriate compartments by the active transport mechanism.

The electrical impulse is transmitted from cell to cell by a chemical transmitter at the synapse. The steps involved in this process include synthesis of the chemical, its storage, release by appropriate stimuli, diffusion across the synaptic space, attachment to a receptor on the post-synaptic membrane and enzymatic degradation.

III EFFECT OF ETHANOL ON ACTIVE CATION TRANSPORT

Because of the importance of active cation transport in maintaining ionic concentration gradients and therefore the excitability of the cell, the work in this laboratory has concentrated on the effects of alcohols on a number of systems with high levels of active cation transport.

a) Frog skin

The frog skin transports Na^+ actively from the outside to the inside. This transport generates a current which can be measured by applying an external current of opposite charge, sufficient to neutralize it. The mag-

nitude of this neutralizing current, which can be readily measured, is equal to that generated by the movement of Na^+ across the skin.

It is found that ethanol in concentrations from 100-1600 mg./100ml. produced a dose-dependent depression of Na^+ transport varying from 5-50% at the extremes of dosage used[4]. The possible mechanisms by which this effect could be produced were considered:

1. interruption of energy supply to the transport system.
2. impairment of access of Na^+ to the transport carrier.
3. impairment of the transport mechanism itself.

The first possibility was discarded because of the rapidity of the ethanol effect. This was produced in only 5 seconds, whereas high concentrations of cyanide required about 5 minutes to depress Na^+ transport. The other two possibilities were studied in other systems.

b) Tissue slices

Both brain and kidney tissue have high levels of active cation transport. These organs can be removed from an animal and slices weighing 25-60 mg. can be cut. The slices are incubated anaerobically in Ringer's solution for 10 minutes during which period they lose K^+ to the medium. At this point oxygen is bubbled through the medium and the slices start to reaccumulate the lost K^+. The effect of ethanol on K^+ reaccumulation during this period of aerobiosis was studied in guinea pig brain slices and rabbit kidney slices[5].

It was found that ethanol did not affect the loss of K^+ from the slices during anaerobiosis. At a concentration of 400 mg./100 ml. ethanol inhibited the active reaccumulation of K^+ by 45% in brain slices during aerobiosis. Similar results were obtained in kidney slices.

This inhibition is not likely to be due to impairment of access of the cations to the carrier system because the passive diffusion of K^+ during anaerobiosis was not affected by ethanol. Therefore, considering the results obtained with the frog skin and the brain slices, it seemed most probable that ethanol was inhibiting cation transport by interfering with the transport mechanism itself.

c) Mg^{++}, Na^+, K^+-activated adenosine triphosphatase (Na^+, K^+-ATPase)

A great deal of evidence has accumulated suggesting that a Na^+, K^+-ATPase is part of the system responsible for the active transport of Na^+ and K^+[6]. The ATPase system and the cation transport mechanism have several unique biochemical properties in common[7] and the distribution of the ATPase inside cells and in various cells of different tiissues and organisms parallels the level of active cation transport in these cells[8].

Most of the Na^+, K^+-ATPase is recovered in the microsomal fraction of the cell. This fraction was prepared from rat, guinea pig and human brain and electric organ of the eel. Basically, the cells were disrupted by homogenization and the fractions were separated by differential centrifugation. The microsomal pellet was sedimented at 100,000 x g for 30 minutes. The ATPase activity of the resuspended pellet was assayed and the effect of ethanol on it was determined[9].

For this enzyme to be active Mg^{++}, Na^+, K^+ and ATP must be present in the incubation medium. In the presence of constant concentrations of Mg^{++}, Na^+ and ATP the activity increases with increasing K^+ concentration. Therefore kinetically, K^+ may be considered a substrate for this enzyme although it is actually a co-factor. Ethanol was found to inhibit the enzyme but the percentage inhibition decreased with increasing K^+ concentration. On a Lineweaver-Burke plot of 1/activity against $1/K^+$, the graph was that of a classical competitive inhibition between ethanol and K^+ (Fig. 1). Identical results were obtained from rat, guinea pig and human brain and from the electric organ of the eel.

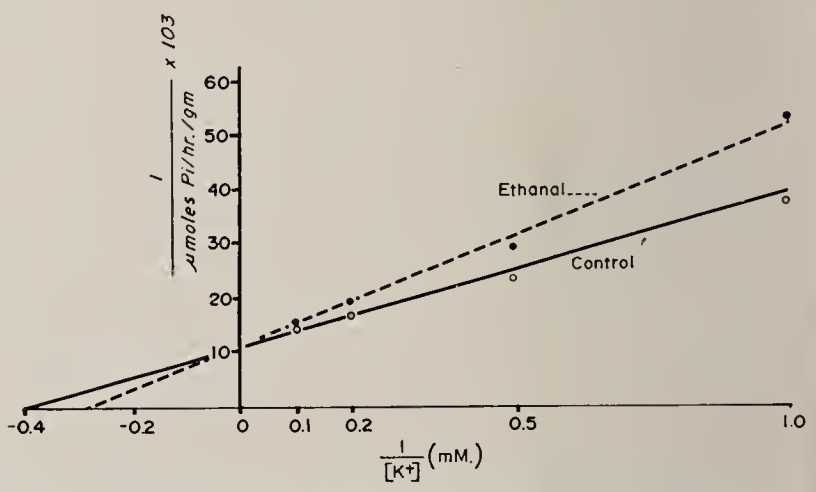

Fig. 1: Lineweaver-Burke plot showing antagonism between ethanol and K^+ in the microsomal ATPase from a sample of human brain.

These results confirm the previous impression that ethanol inhibits active cation transport by inhibiting the probable enzymatic basis of this transport system.

Since the effect of ethanol on the Na^+, K^+-ATPase was antagonized by K^+, we investigated the effect of K^+ on the degree of intoxication produced in rats by intraperitoneal injection of ethanol. The degree of intoxication was measured by the inclined plane method[10]. The animals were put on a hinged board whose free end could be raised by motor and pulleys from 0 to 90° at a constant angular velocity. The angle at which the rat begins to slide down the board is measured. This angle is decreased when the rat is intoxicated and the extent of this decrease is taken as an index of the degree of intoxication.

The results showed that when KCl was administered with the ethanol the rats were less intoxicated than when they received NaCl with ethanol. The differences were statistically significant at the $p < .025$ level. Neither KCl nor NaCl alone had any effect on the performance.

These results suggest that intoxication, like the ethanol effect on the ATPase system, may be antagonized by K^+. This is therefore compatible with the belief that at least part of the manifestation of alcoholic intoxication is due to inhibition of this enzyme system.

IV DISCUSSION

It seems highly unlikely that K^+, a polar, hydrated cation, and ethanol, a relatively non-polar molecule, would be competing directly for the same active site of the ATPase. It is more likely that the antagonism is indirect. K^+ presumably occupies a hydrophilic site on the enzyme, whereas ethanol probably interacts by H-bonding and Van der Waals attraction with a primarily lipophilic site on either the same protein or adjacent protein or lipid molecules. This interaction may affect the configuration of the ATPase protein, resulting in a reversible distortion of the active K^+ site such that K^+ no longer fits into it.

This effect of ethanol is probably not a specific one but rather a manifestation of the non-specific interaction of alcohols with the cell membrane. Other aliphatic alcohols produce the same effect and their potency is proportional to their thermodynamic activity[11]. Other effects of ethanol such as decreased release of acetylcholine from brain slices[12] and decreased Na^+ conductance during the action potential[13] may well be manifestations of this type of interaction with the cell membrane.

The consequences of inhibition of Na^+ and K^+ transport will lead to depression of the nervous system. In the resting neuron, the intracellular K^+ concentration will decrease and the K^+ concentration gradient will decrease. This will make the membrane potential less negative and the cell will initially become hyperexcitable, because a smaller stimulus will suffice to produce the critical depolarization for an action potential. With every impulse the cell loses K^+ and the concentration gradient is diminished still further. Eventually, therefore, under the influence of ethanol, the membrane potential cannot be maintained above the critical level for depolarization and it becomes inexcitable.

The effect of alcohol in decreasing Na^+ conductance during the action potential[11] results in a decrease of the height and rate of rise of the action potential. The increased K^+ conductance during repolarization is unaffected by alcohols; therefore, some alcohols may hyperpolarize the membrane and make the cells less excitable.

The action of ethanol in decreasing the release of acetylcholine from brain slices will also help to depress the nervous system because electrical impulses will be transmitted less efficiently. If this takes place at each synapse in a poly-synaptic pathway, considerable impairment could result.

V SUMMARY

Ethanol acts primarily on the reticular formation which contains a complex interconnecting system of inhibiting and excitatory neurons and synapses. Ethanol probably interacts nonspecifically with these cell membranes. This produces several important results such as inhibition of active cation transport, depression of the increase in Na^+ conductance associated with depolarization and decreased release of acetylcholine at synapses. All these effects could contribute to the picture of alcoholic intoxication.

The ultimate goal of this line of investigation is to understand the mechanisms by which addiction to alcohol evolves and thereby provide a rational basis for prevention and therapy. Since our experiments suggest that the acute effects of alcohol are due at least in part to depression of active cation transport, we are now investigating whether changes in this transport can be correlated with the development of tolerance and addiction to alcohol.

I. Laufer 6T7

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Psychedelics And Addiction – LSD And Marijuana

A. Chaiton 6T9

INTRODUCTION

There is a sad lack of general knowledge and much misunderstanding about drugs likely to lead to addiction, about persons who become addicted to various drugs, and about the process of addiction itself.

Now, drug dependence is defined as a state arising from repeated administration of a drug on a periodic or continuous basis. It is a term applicable to all types of drugs and its characteristics will vary with the agent involved. All dependence-producing drugs are capable of producing a psychic drive which requires periodic or chronic administration of the drug for pleasure or to avoid discomfort. This is termed psychic dependence and it may be the only factor involved in perpetuating the compulsive abuse. Some drugs also induce physical dependence, an adaptive state characterized by intense physical disturbances when administration of the drug is suspended or its action is counteracted by a specific antagonist. These disturbances, the withdrawal or abstinence syndrome, display a specific spectrum of signs and symptoms of a psychic and physical nature characteristic of each drug type.

Many drugs induce a form of adaptation in the individual known as tolerance. This state is characterized by a decreased response to the same dose and the need to increase the dose in order to obtain the same biological effect previously exhibited. It is important to note that drug dependence and abuse may occur without tolerance[24].

With this general framework about the concepts involved in drug abuse, we can go on to a discussion of the psychedelics, LSD-25 and marijuana commenting on their relationship to the so called "addictive drugs".

PSYCHEDELICS

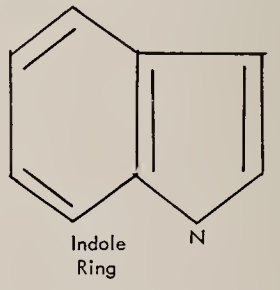
Drugs such as LSD and marijuana, which induce very diverse phenomena naturally have many names. They are generically termed hallucinogens although true hallucinations are rarely encountered. Most visual phenomena experienced are actually illusions—errors in seeing based on some sensory cue. Psychotomimetic is a term denoting drugs that induce symptoms imitating psychoses. Psychedelic, meaning mind-manifesting is a word coined by Osmond to include all drugs whose primary action is alteration of the psyche. The nature of the disturbance is not specified; consequently, this is a broader and more satisfying descriptive name.

1. CHARACTERISTICS

Examples of the more potent psychedelics are LSD, mescaline, psilocybin, Ditran and Sernyl. Marijuana also belongs to this class of drugs, and perhaps because it is rather weak, it is the most widely used of all[7]. The drugs have in common an ability to induce sharp changes in states of awareness, perception, self-perception, self-communication and communication with others — changes which are exquisitely dependent on the situation and the social setting in which these drugs are given[10]. Savage and others[19] believe that the hallucinogens do not produce experiences de novo but inhibit repressive mechanisms that ordinarily operate and simply allow subjects to explore the contents of their own minds.

2. CHEMISTRY OF PSYCHEDELICS

Most of the psychedelics contain the indole structure:



Of course not all indoles are psychedelics; but, of all the naturally occuring psychedelics only the cannabinols, the active principles from hashish (marijuana) are not indolic. Why the cannabinol and indole structures should produce similar mental states is still unknown[6].

SUBJECTIVE EFFECTS

The subjective effects of the psychedelics, is above all others, the major reason why people take the drugs either criminally or therapeutically. There is no limit to what normal people may experience when they have taken a psychedelic. Despite the great variation seen, a consistent group of effects can be observed on administration[9]. Perceptual and visual changes are most prominent. Space is very commonly distorted, becoming smaller and large in pulsations. As subjects walk, objects passing by become large too quickly and subjects have the impression that objects exploded into their field of vision. Long corridors become interminably long. Very common is an unusual change in the size of one's hands or feet. They appear to pulsate by getting larger or smaller. Lines and patterns became wavy or distorted. Illusions and hallucination are common. Usually the subject is aware that they are such, but occasionally

during moments of panic they may develop a frightening reality. There is an increased auditory acuity. There is distortion of kinesthetic sensation. Subjective time becomes completely altered. It stops, becomes slow, runs backward but more often accelerates. Moments seem years. Euphoria is prominent. Synesthesia is often reported i.e. the cross over of sensation from one sense modality to another e.g. subject will, "hear colours", or "scent music"[6].

It is the subject's interpretation of these fundamental psychedelic effects, which gives rise to the wide spectrum of psychedelic experiences. Everyone has been impressed by the way factors apart from the drugs themselves, modify the experience. Some of the more important variables are: the personality of the individual; his current life situation: the attitude of those in contact with him during the experience; the setting; and, the reason why the drug is taken and given. In the light of these variables it can be seen how psychedelics can elicit experiences which may be terrifying and disorganizing or pleasurable and meaningful[6].

Unfortunately, the "bad trip" or "freakouts" are more probable in those who have the greatest desire to take the psychedelics: the very young, the emotionally immature or unstable, the deeply depressed and borderline schizophrenics. Psychiatrists and drug researchers usually exclude such persons from therapy or experimentation. Black marketeers, however, apply no such exclusion. There is considerable evidence that for some individuals LSD and related substances can produce serious untoward psychological effects. Until susceptibility to such adverse reactions can be detected in advance, and until the therapeutic value of the drugs has been established, their uncontrolled use to provide an unusual experience should be strongly discouraged[12].

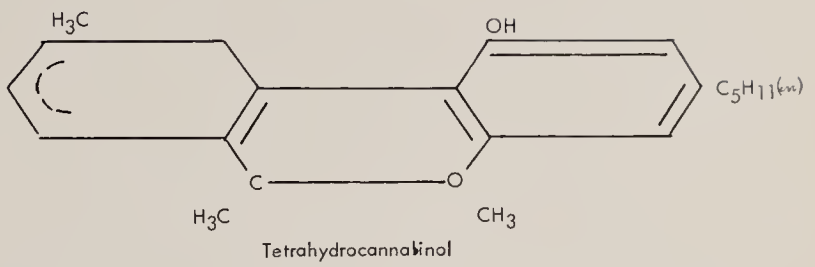
CANNABIS (MARIJUANA)

1) ORIGIN

Cannabis is obtained from the flowering tops of female hemp plants, of the species Cannabis sativa. The resinous exudate from the top of the plant contains most of the active ingredients. In the Middle East and Africa this exudate is called hashish, while in the United States the term marijuana is used to refer to any part of the plant or extract therefrom which induces somatic and psychic changes in man[11].

2) CHEMISTRY

The principal constituents of hashish are the cannabidiols, cannabinol and the tetrahydrocannabinols. It is now believed that the most active ingredient in cannabis is a tetrahydrocannabinol, which has the following structure:



Tetrahydrocannabinol

Many derivatives have been synthesized and studied and some of these derivatives are more potent than the natural plant products.

The content of the cannabinolic constituents in the hashish resin depends to a large extent on the conditions of growth of the plant. This is the source of one of the major problems in studying cannabis. Not only are we dealing with mixtures of unknown potency and constitution, but the bioiogical activity of even pure tetrahydrocannabinol depends on its isomeric make-up. In addition, the low solubility of its active principles makes it hard to study in acceptable solvents[5].

Few plant products are so variable and unpredictable in their effects as cannabis and its extracts. We are dealing with mixtures of active and less active chemical compounds, some of which may have their activity modified by their partial combustion when smoked. These are only some of the problems that must be dealt with in considering hashish dependence.

3) PHARMACOLOGY OF CANNABIS

(a) Administration

The methods of administration vary with different societies. In the West the most common way of assimilating hashish is the smoking of the resin in combination with tobacco leaves, as a cigarette, whereas a hookah is the most common Eastern style of smoking it[5]. Chewing or swallowing cannabis preparation is very prominent in India. It has been found that the effects produced after oral intake persist longer than those following inhalation (smoking)[20].

When the drug is taken by inhalation of its smoke, effects occur within a few minutes and are relatively short-lived; after ingestion, ½ to 1 hour may elapse before onset of effect, and the influence may persist for 3 to 5 hours. There are no lasting ill effects from the acute use of marijuana and no fatalities have ever been reported. There is a remarkable similarity between large dose effects of marijuana and the effects of LSD —25, mescaline and psylocibin[11].

(b) Subjective and Physiological Effects

Cannabis is used to evoke pleasure and other subjective effects and for alleged enhancement (or distortion) of perception and performance[24]. Of all the actions of cannabis resin it seems that the most commonly observed symptoms in man are the euphoric effect, the fragmentation of thought and hallucinations[5]. The subjective effects, although milder than LSD, have already been discussed in greater detail under psychedelics. The

exact response depends on the basic personality and temperament of the subject, the dose, the route of administration and the specific circumstances in which the drug is used. Thus, great variation between subjects is seen[11].

The physiological effects have been comprehensively studied by Allentuck[2]. There is usually an increase in pulse rate and blood pressure. Conjunctival vascular congestion, vomiting and diarrhea have also been noted. A marked increase in appetite and hunger are said to be characteristic[11].

The exact mechanism of action of cannabis is still under investigation. Some effects e.g. hypothermia and respiratory paralysis can be attributed to a direct effect on the C.N.S.[3]. The depression of I^{131} uptake by the thyroid may be centrally or peripherally explained[5]. Other effects, such as prolongation of sleeping time induced by barbiturates[14] are probably due to a direct effect of the resin on central nervous system enzymes activity. This is a probable underlying explanation for most events. Other fields of interest include the problem of tetrahydrocannabinol metabolism and the activity of the metabolites[5].

(c) Relation to Addicting Drugs

In the opinion of the Commission on Narcotic Drugs (1962), "The abuse of this drug (cannabis) is more widespread throughout the world than the abuse of any other single drug." But to what extent can we relate marijuana to other addicting drugs with respect to the dangers and characteristics of the addictive process? Some authorities go to the extent of saying that the only link with narcotic drugs is that marijuana is illegal[10]. Abraham Wikler states that there is no definite evidence that tolerance and physiological dependence develop during continuous use of marijuana. He concludes that marijuana is less addicting than drugs of the morphine type[25 26].

The Expert Committee on Addiction-Producing Drugs[23], has defined drug dependence of cannabis type clearly as habit-forming. The habit is gregarious and is easily abandoned. The Brain Committee[22] considers cannabis not a drug of addiction but an intoxicant. It does not give rise to biological dependence and withdrawal symptoms and its psychological dependence is not considered as strong as that of tobacco or alcohol.

It is evident that society's perspective on marijuana is changing. As recently as March of 1966, a subcommittee of the Medical Society of the County of N.Y. reported that, "Marijuana . . . should be removed from the opiate-cocaine category". The White House Conference on Narcotic and Drug Abuse in 1962 declared:

"It is the opinion of the Panel that the hazard of marijuana per se has been exaggerated and that long criminal sentences imposed on an occasional user or possessor are in poor social perspective."

We can conclude by saying that hashish has no withdrawal effects and seemingly does not produce tolerance, but its consumption may lead to a certain psychological dependence syndrome.

LYSERGIC ACID DIETHYLAMIDE

1) ORIGIN

D-Lysergic acid diethylamide is one of four stereoisomeric alkaloids which can be synthesized from lysergic acid, but it is the only one which exhibits unusual psychological effects as first discovered by Hofmann in 1943. There are two important sources of LSD; ergot, known as a poison or toxin for many centuries, and the morning glory plant.

Ergot is the rhibomorph of Claviceps purpurea, the parasitic fungus which grows in the heads of members of the grass (Gramineae) family. Rye is the principal plant thus infected.

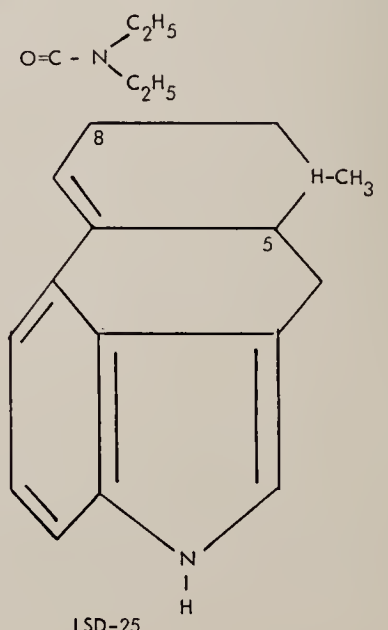
Rivea corymbosa (ololiuqui) is one of the semitropical varieties of the huge morning glory plant. The use of two varieties aptly called "Heavenly Blue" and "Pearly Gates", is expanding to-day. As early as 1570 Francisco Hermandez first described ololiuqui, the narcotic of the Aztecs. R. corymbosa contains two active fractions:

(a) a glucoside first isolated by Cook and Kieland[8] of unknown structure

(b) ergot alkaloids, among which D-lysergic acid is the most powerful hallucinogen.

2) CHEMISTRY

Lysergic acid diethylamide or more properly, d-lysergic acid diethylamide tartrate is also called LSD—25 and Delysid. The LSD part of the abbreviation is from the German, Lyserg Saure Diethylamid. The "25" indicates that it was the 25th in a series of analogous compounds synthesized in the Sandoz laboratories. The chemical structure of LSD (or LSD-25) looks formidable but it is indolic and has the same $CH_2.CH_2.N(CH_3)(CH_3)$ "tail" as psilocybin, DMT and other hallucinogens[6].



LSD-25

Carbons five and eight are asymmetric and four isomeric, optically active isomers are possible and are known. Some approach but never exceed LSD in potency.

3) PHARMACOLOGY

(a) Administration

The dosage of drug which may be taken orally or by injection varies from 25 mcg. to 1,000 mcg. If a normal dose of 100 mcg. is taken oraly, the onset of its effects may be felt within forty-five minutes. The effect begins to recede four hours after consumption and terminates in six to twelve hours. The course is different for different methods of intake. With the recent widespread and more casual use of hallucinogens we find LSD peddled in pills, ampoules and sugar cubes saturated with 100 mcg. for a market price of $1.00 to $10.00 each[6].

LSD is rapidly absorbed after oral administration and is distributed widely throughout the body. Distribution studies with C^{14} labeled LSD have indicated a concentration in the liver, which suggests a rapid metabolism. It appears to be excreted by the liver in the form of 2-oxy-LSD[4].

(b) Effects

The toxicology of LSD has been reviewed by Rothin and Cerletti[16] and Rothlin[17]. LSD is so powerful that doses given to humans are a very small fraction of the hypothetical toxic dose. From a physiological point of view, it is not a toxin for the human body when recommended doses are used. No deaths directly attributable to the drug are known and no serious physical complications are reported. By and large the psychotic state produced by LSD appears to be reversible, but cases presumably resulting in permanent psychosis have been reported and are thought to have been latent. Other effects have been discussed under psychedelics.

(c) Mechanism of Action

The mechanism of action of LSD is still in dispute; although numerous hypotheses have been put forth and investigated. The reader should refer to Hoffer for a concise review of the mechanisms mentioned[9]. Certain direct effects of LSD have been postulated. It could influence the nerve cell by blocking energy production, by altering cell membrane permeability, by reducing the blood supply to local or general areas of the brain or by increasing permeability of the blood brain barrier and so allowing toxic substances to enter. It could alter synaptic transmission by being a competitive inhibitor or by facilitating the direct action of some neurohormones such as serotonin, noradrenaline, adrenaline, or histamine. The sympathetic and parasympathetic effects of LSD may be explained by its indirect action e.g. it may alter the concentration of other essential substance producing a major change in some other biochemical system. More work is needed to confirm or disprove speculation on its mechanism of action.

(d) Therapeutic Value

The use of LSD in the treatment of alcoholism is discussed in another paper in this journal.

(e) Addictive Potential

Tolerance is very rapidly developed and for therapeutic purposes, successive sessions are spaced at intervals to accommodate this factor. The hallucinogenic effect of a second dose of LSD is almost eliminated if it is given within 24-48 hours after the first. Cohen reports that three days of abstinence was necessary to remove the tolerance gained by three days of normal dosages[6]. Cross-tolerance to mescaline and psilocybin as well as to other lysergic acid derivatives has been demonstrated.

A committee of WHO reported that the extent of psychic dependence was not yet clear, but that there was no evidence of physical dependence[24]. Jarvik reports no physical dependence or abrupt withdrawal symptoms and concludes that its use may be considered drug abuse but not addiction in the sense that an overwhelming preoccupation with its use or a compulsion to continue its use does not occur[12]. Cohen warns that although true addiction has still not been recorded it can be definitely stated that habituation to the psychological effects of this drug is possible in certain personality types. Passive-dependent and psychopathic individuals with access to large supplies have taken them uncounted times and have had difficulty in breaking themselves of the habit[6].

CONCLUSION

As it can be argued that a thing has neither intrinsic good nor evil in it, but the manner of use determines its value, so it can be said that the psychedelics are neither good nor bad drugs. While reports of prolonged mental illness following their use have appeared not infrequently, in other cases these drugs have assisted the marked improvement in the pathological behaviour patterns of addicts. Moreover, these drugs have provided us with new knowledge about the psychology and physiology of perception. But now, the psychedelics are becoming freely available via the black market to anyone who wants to take these potent agents for "kicks" or for "mystical experience". It is in the context of encouraging the good uses of these drugs by qualified investigators and discouraging their bad uses by an indiscriminate public that legislation should be enacted. Neither complete prohibition nor a complete lack of protective regulations would be appropriate.

ACKNOWLEDGEMENT

I would like to express my appreciation to Dr. H. Kalant, Professor of Pharmacology for his helpful comments.

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Special Report:

Quebec Beer Drinkers' Myocardiopathy

A Report of the Laval University Conference

Between the months of August 1965 and February 1966, forty-eight heavy beer drinkers in Quebec City developed a syndrome characterized by severe, rapidly progressive myocardial failure, without chest pain. Twenty of these patients died. A conference to exchange and disseminate information about the new syndrome and to discuss possible causes was held at the Faculty of Medicine, Laval University, on May 25, 1966.

It was revealed that the most freqent symptoms found among the drinkers were dyspnea, abdominal pain, orthopnea, ankle edema, asthenia, anorexia and nausea. The signs most frequently encountered were tachycardia, cyanosis, tachypnea, gallop rhythm and pulmonary râles.

Cardiographic changes, although non-specific (tachycardia, P wave abnormalities, low voltage QRS complexes and raised S-T segments) showed a pattern distinct from either beri-beri heart or the alcoholic myocardiopathy described by William Evans.

Radiological findings were only the non-specific changes of heart failure. Biochemical tests indicated liver function abnormalities most likely secondary to the cardiac decompensation. Hemodynamic studies showed that there was no good correlation between the degree of decompensation and the clinical state of the patients.

Light microscopic study of the post mortem sections of diseased myocardium showed separation of muscle fibres by edema, fatty changes and a surprising absence of evidence of inflammation. Electron photomicrographs revealed abnormal mitochondria.

Epidemiologists established that the stricken drinkers consumed up to 9 litres (25 small bottles) of beer per day and never strictly limited themselves to any one brand of beer. Although other possible causes were discussed, it was considered most likely that the myocardial damage was due to substances in the beer. The enzyme, papain, which is used in the brewing process, and cobalt salts which were recently added to one Quebec beer in order to stabilize the foam were most strongly implicated. Acute toxicity studies in animals by the Food and Drug Directorate, employing various components of the beer had not yet, at the time of the conference, produced definitive results.

Although the participants in the conference refused to draw conclusions from the evidence available at that time, it seemed to this observer that the cobalt salts, employed initially, prior to the first reported cases and then discontinued with the subsequent cessation of new cases, were the etiological factors.

Michael Schwartz 6T7

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A transcript of the conference, in French or English, is available from Dr. Yves Morin, Cardiovascular Lab., Hôtel-Dieu, Quebec 4, P.Q.

The Smoking Habit

L. Lacey 6T7

Despite public awareness of the numerous reports concerning the association between smoking and certain serious diseases, smoking is still a popular and widespread habit. With this fact in mind, the following article will summarize the deleterious effects of tobacco smoking, and what is known about the habit itself. Finally, the methods used to help smokers stop will be discussed.

Pharmacology

Over five hundred compounds have been identified in cigarette smoke. Four main groups of toxic substances are recognized[14]:

1. Nicotine
2. Carbon monoxide and prussic acid (two gases which impair tissue oxygenation).
3. Irritant gases (e.g. ammonia, phenols)
4. Tars, arsenic, chromium and nickel, (all of which are agents capable of inducing cancer experimentally).

Among the "tars" isolated from cigarette smoke, seven polycyclic hydrocarbon compounds have been shown to be carcinogenic in laboratory animals. However, the total tar from cigarettes has many times the carcinogenic potency of these seven compounds alone. It is thought that phenols and fatty acids present in the cigarette smoke act as "co-carcinogens", i.e. enhance the cancer producing effects of the carcinogens.

Nicotine causes stimulation of the central nervous system in the amounts usually absorbed by smoking, and it is this effect which provides the pharmacological basis of the smoking habit. In higher doses, nicotine causes C.N.S. depression, tremor and neurogenic vomiting. Such effects may be seen in those who are not used to smoking. Other acute effects of nicotine include increased serum lipids, inhibition of vitamin C absorption, decreased appetite, increased blood pressure and heart rate, and cutaneous vasoconstriction. This drug, being rapidly detoxified by the liver, is unlikely to cause any chronic health problem.

Pathology

Histological changes in trachea and bronchi are more frequent in smokers; these include:

1. loss of cilia
2. hypertrophy of bronchial mucous cells
3. basal cell hyperplasia
4. appearance of atypical cells.

The first two changes are thought to be related to chronic cough and sputum production, and the last two changes are considered pre-malignant[14].

Cigarette smoking contributes substantially to mortality from certain specific diseases and to the overall death rate. The death rate for those smoking over forty cigarettes per day is one hundred and twenty percent higher than for non-smokers, and for those smoking twenty cigarettes per day the death rate is about eighty percent higher. At age fifty, a smoker of over a half pack per day has a reduction in life expectancy of almost five years[9].

The following specific conditions are considered related to cigarette smoking:

1. chronic bronchitis and emphysema
2. coronary artery disease
3. cancer (by site)
   (a) lung cancer
   (b) oral cancer
   (c) lip cancer (especially in pipe smokers)
   (d) cancer of the larynx
   (e) cancer of the esophagus (suspected but not proven)
   (f) cancer of the urinary bladder. In 1965 Kerr et al of Toronto noted that a statistical relationship between smoking and cancer of the bladder had been established. They then showed that smoking, by inhibiting tryptophane metabolism, caused a build-up of carcinogenic metabolites which were excreted in urine[12].
4. delayed healing of peptic ulcers, especially gastric ulcers.
5. reduced weight of babies born to smoking mothers.
6. tobacco amblyopia (unexplained dimness of vision in pipe and cigar smokers). This condition has been suspected clinically but not proven.

The mortality ratios (ratio of observed deaths among smokers over actual deaths occurring among non-smokers) for smokers was particularly high for a number of diseases[14]:

cancer of the lung	10.8
bronchitis and emphysema	6.1
cancer of the larynx	5.4
oral cancer	4.1
cancer of the esophagus	3.4

Habituation

In precise terminology, the smoking habit should be labelled "habituation" rather than "addiction". This distinction is based on the fact that there is a psychic, but no definite physical dependence. There is no tendency to increase the dose in order to maintain the effect, and there is no distinct withdrawal syndrome.

Pharmacological basis of habituation

Only nicotine has been given serious consideration as being important in producing the tobacco habit. Many,

but not all smokers, can detect a reduction in nicotine content of cigarettes. The injection of nicotine produces subjective effects similar to those of inhaling cigarette smoke, and the urge to smoke is greatly reduced during nicotine administration[14].

Different subjective effects are described for smoking. Most smokers describe a tranquilizing effect, but many describe a stimulating effect in that it serves as an early morning "pick-up" or relieves depression. Why the predominant subjective effect is tranquilizing while the pharmacological effect (as described above) appears to be stimulating is not yet explained.

Cigar and pipe smokers do not inhale and tend to feel more tranquilizing effects from smoking. Heavy cigarette smokers who do inhale describe smoking as a pleasant sensory experience. It may be that inhalation and consequent irritation of bronchial and pulmonary tissues act as pleasant stimuli countering the usual subjective effect of tranquilization.

No characteristic withdrawal syndrome has been demonstrated. Fear of an unpleasant withdrawal syndrome is often important in keeping true addicts from stopping their habit. Many symptoms may occur following cessation of smoking, but these are of such varied nature as to suggest more of an emotional reaction to deprivation. The usual withdrawal symptoms noted are irritability, anxiety, impaired concentration and judgment, ritualistic patterns such as tapping, pacing, and frequent eating. Nausea, epigastric distress and tremor, also occur in some cases. The duration of these symptoms varies from days to months, and varies in intensity from time to time. This is thought to be inconsistent with any drug withdrawal. In contrast, during addiction to narcotics, certain enzyme systems are inhibited and the development of tolerance is characterized by increased synthesis of these enzymes. Subsequent withdrawal of the inhibiting narcotics results in an excess of this enzyme activity producing a typical constellation of withdrawal symptoms with clearly defined onset and decline.

There is a varying susceptibility to nicotine on an inherited basis, such that some individuals cannot tolerate smoking at all. Some tolerance does occur with repeated use. Effects such as nausea and vomiting frequently occur with initial use but later disappear. Nicotine, unlike morphine, does not cause adaptive changes to occur in the cells, and all smokers soon find a limit to their intake. A form of tolerance occurs in the sense that habitual smokers will accept persistent cough and bouts of nausea, which would be unacceptable to the novice.

Some Psycho-social Factors

As mentioned, many different reasons are given by smokers to explain their habit. Most say "It relaxes me" (49%); it reduces tension and helps them to concentrate. Many derive comfort in social situations and find smoking gives them poise or helps them express themselves better (48%). A third major reasons given for smoking was for the flavour (20%). Probably no one reason can be found to explain why people smoke, different effects are described according to the smoker's psychological needs[2].

Among social factors, whether or not the parents smoke is considered important. If both parents smoke, one third of the children are likely to smoke, but if neither parent smokes, only one sixth of the children are likely to smoke. There is also a higher incidence of smoking among those whose siblings smoke; however, most non-smokers state they were influenced mainly by their parents (others state they were influenced by health reasons or by deriving no enjoyment from smoking). At the same time, the non-smokers report significantly less parental opposition to smoking than do smokers[15]. This may relate to the idea that adolescent rebellion is a factor in initiating smoking.

Peer group pressures, however seem to exert more influence in the beginning of smoking than does parental example. Just as smoking marijuana or taking L.S.D. usually implies belonging to a clique of fellow addicts, many a smoker begins the habit in order to conform to his friends in school or work circles. Members of the "proselytizing smoking fraternity" not only introduce the novice to this habit but also, by their example, hinder his attempts at quitting.

Dependence on potent drugs is usually based on serious personality traits. Although such a statement would not be made about tobacco users, some researchers do suggest smokers and non-smokers may show differing personality traits. Some studies go even further and seem to stress differences between light smokers and heavy smokers as well.

Eysenck[6] shows strong correlation between cigarette smoking and extroversion. Extroverts, he believes, have a "stimulus hunger" and seek the stimulating effects of nicotine. Extroverts also indulge more in coffee, alcohol, spicy foods, illicit sex, impulsiveness and risk taking. He found no relation between smoking and neuroticism (emotionality). Other studies claim that, among those who smoke more, there are higher divorce rates, and more frequent changes of jobs.

One study claims that there is a greater incidence of orality among smokers[10]. Heavy smokers who tried to stop and failed had had the shortest experience of nursing at the breast. If the mothers were controlling, cold and harsh when the individual was a child, the individual remained preoccupied with oral intake activities. Another study notes that forty percent of former smokers need some "oral" substitute such as eating, chewing gum, or nail biting[2]. Twenty percent of former smokers flatly denied any substitute was desired, suggesting that orality is not a universal factor.

The fact that smokers continue their habit despite awareness of the smoking—lung cancer, or smoking—life expectancy statistics is intriguing. Most psychologists

state that the practice and the belief being dissonant will produce anxiety unless one or the other is rejected. Hilgard states: "If the decision is made to continue smoking, the dissonance will be reduced by disbelieving the information about the relation between smoking and lung cancer; if the decision is made to give up smoking, the information will be stoutly defended"[15]. In one study conducted after the publication of the Surgeon General's report, more former smokers (100%) believed in the relationship between smoking and lung cancer than did non-smokers (74%), while fewer current smokers (67%) believed this information. Furthermore, doctors are smoking less (Great Britain, Massachusetts); in Massachusetts 52% of doctors smoked in 1954, but only 23-33% smoked in 1964[7]. Apparently doctors feel more compelled to accept such authoritative medical reports and also are more exposed to them.

Breaking the Habit

An action repeated a dozen or more times a day for most of one's life is obviously difficult to stop. Most popular methods of aiding the quitter are classed as educational, psychotherapeutic, or pharmocological.

A massive anti-smoking campaign in Edinburgh in 1958 failed to increase the proportion of non-smokers or even to reduce the proportion of heavy to light smokers to any significant degree[7]. Statements by the Royal College of Physicians and Surgeons in Britain and the U.S. Surgeon General of Public Health caused only temporary declines in tobacco consumption. One possible effect of increased information, the decline of smoking among doctors, has already been mentioned.

Group therapy usually plays an important part in smoking clinics, along with other methods. Group therapy alone has also been tried with some success. Lawton[13] who attempted group therapy alone, noted that only three out of seventeen patients continued to abstain eighteen months after the therapy sessions. His suggestion that periodic reinforcement of the wish to abstain was necessary may be applicable to all forms of treatment[13].

A wide variety of pharmacological agents have been used[7 16]. Local anaesthetics or astringents have been used to eliminate the taste of smoking. Anticholinergics have been used to dry the mouth and thus make smoking unpleasant. Tranquillizers and stimulants are popular adjuncts. In restless patients, barbiturates and meprobamate are used. In patients who miss the stimulating effect of nicotine, caffeine, metrazole or amphetamines are used.

Another popular groups of drugs are the nicotine substitutes such as Lobeline. This drug has some pharmacological properties in common with nicotine and is given as four mg. of "Lobidan" (a buffered form of Lobeline) up to four times per day. Clinical trials of this drug are contradictory, some showing Lobeline has no more effectiveness than a placebo[16].

Most smoking clinics show rather poor long term results. In Stockholm, 76% of smokers stopped after ten days at a smoking clinic, but only 23% were not smoking after six months. Other clinics had similar results. Several factors have been found to be related to the likelihood of relapse. More smokers relapse to their former rate of cigarette smoking if they try to reduce smoking rather than stopping, or if they switch to cigars or pipes. There is less likelihood of relapse the longer one abstains (after one year, 37% relapse; after two years, 5% relapse). There is also a higher rate of relapse among those who started younger and among those who inhaled.

SUMMARY

Clinicians in a wide variety of medical fields require a knowledge of the pathological effects of smoking and also a knowledge of the habituating factors so that appropriate preventive measures can be carried out.

The habituation to tobacco is a "habit" rather than a true "addiction". Although the pharmacological effects of nicotine have varying force in this habit, greater emphasis is placed on such psycho-social factors as tranquillization, social role-playing, parental and peer group example, and possibly personality traits.

Despite the wide variety of therapeutic measures which have been tried in helping smokers to break their habit, results have not been encouraging.

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Recent Advances

Hospital For Addictive Diseases

It is probably true that the problem of addiction, be it to alcohol or drugs, is as old as mankind. Inasmuch as it is a problem, we are bound to try and find a solution, but inasmuch as the problem has existed for so many generations, it is too easily taken for granted and dismissed. One's views of the alcoholic or addict tend to be culturally defined rather than medically orientated, and when this is coupled with the prospect of an unremunerative, unco-operative patient, it is not surprising that so little has been accomplished.

In the past, such work as has been done in this area, has been accomplished by interested individuals and a handful of organizations such as the Alcoholism and Drug Addiction Research Foundation, Alcoholics Anonymous, the Bell Clinic, and the Salvation Army. Against this background, the plans revealed within the past two months to construct a 100-bed hospital for research on the alcoholic and addicted patient represent a unique and significant step forward.

The hospital is to be built in Toronto on the campus of the University. The beds are to be used strictly for teaching and research as opposed to general treatment, although the hospital is planning an out-patient department to carry 350 patients per day. The teaching facilities of the hospital will be used for post-graduate training and for consultants who are concerned with this type of patient. With the advantages to be gained from intensive study in this area, it is planned that the clinicians and practitioners will return to the undergraduate teaching hospitals so that students may benefit in a practical way from the most recent techniques and theories.

With the availability of research beds, it will be possible to plan a scientific approach to study the problems. A specific statistical population can be set up and controlled. Allowing for personal variation, it is hoped to uncover certain basic principles that are common to the addict or alcoholic. Different programs of treatment can be tried and significant comparisons made. Undoubtedly, there is no one solution but it will be possible to bring together the various disciplines—medical, pharmacological, psychological, sociological—which ultimately are all part of an answer.

In addition to the benefits which can be directly anticipated, there are many indirect advantages. The mere existence of such a hospital will focus attention on the area of alcoholism and addiction. One of the basic problems today is recognizing the sick person. It is estimated that three to four per cent of the adult population over 21 years of age have significant problems with alcohol, yet only 1-2% of this group form the "Skid Row" population[1]. Too often, the problem is masked by social or job status. Perhaps, with the development of new guidelines, the practising physician will be more sensitive to the alcoholic patient and more able to cope with his treatment.

By no means is this advance a final solution to the problem of what to do about alcoholism and addiction. It is to be hoped that it will make the medical profession, as well as the community at large, aware of these conditions as an illness, hence more ready to acknowledge their existence and treat them and, ultimately, eliminate them as medical problems.

W. Cass 6T8

ACKNOWLEDGEMENT

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LSD In The Treatment Of Chronic Alcoholism

The properties of LSD are dealt with in another paper in this Journal. This will be a brief description of how these properties are applied to the treatment of chronic alcoholism.

Will B., who was one of the founders of Alcoholics Anonymous, claimed that he derived the strength and insight to terminate his alcoholism while in the DT's, through a religious experience[1]. In June of 1952, two Canadians theorized that they might produce a religious conversion-type of reaction using LSD-25, while the alcoholic was still in good physical condition, free from the debilitating illnesses that are concomitant with the end stages of chronic alcoholism. In their subsequent therapeutic programmes with LSD, they found that after two years 50% of the patients were abstinent or were very much improved[2].

During the past summer I worked at the Veterans' Administration Hospital in Topeka, Kansas, where LSD is used in conjunction with instruction in problem-solving techniques as the treatment of alcoholics. The pro-

gramme lasted 60 days and the LSD experience was placed near the end of the programme. LSD day is preceded by free discussion on the subject to inform the patient about the drug and how to benefit most from the experience.

On the appointed day, the patient is given 500 mcg. of LSD at 9:00 a.m. and is taken to a specially prepared bedroom. One of the staff sits through the next six hours of the "trip" and gives support and assistance to the patient who is lying with eyes covered. Music is turned on and he is encouraged to let the music carry him away.

There is, of course, great individual variation in reaction to LSD, but for the purpose of scientific description six stages can generally be recognized:

1. The patient experiences a flight of ideas, which he attempts to attribute to external objects.

2. He concentrates on the physiological sensations of headache, nausea and dryness in an attempt to deny the psychological changes which are occurring.

3. The patient tries to rationalize his thinking and is bombarded with sensorial changes and a flood of ideas so rapid that their context is lost. He is confused.

4. Perception is now altered or enhanced—music is felt, colours become more intense and take on new meaning. He realizes that it is the drug and questions the validity of the experience. He feels helpless and incapacitated and tries to hide his inadequacies from the therapist. At this point, he may withdraw or react with hostility.

5. The patient accepts his increased awareness, intellectual capacity and understanding of himself and of others.

6. In the final stage he feels a religious-like rebirth and assimilation into the plan of the universe. It is very individualized and difficult to describe.

The last two levels are labelled "psychedelic". Organization of the "unhabitual perceptions" is necessary and it is the main role of the therapist to give support and guidance. The drug effects need no explanation and are accepted as a reality worthy of further exploration. At this level of stabilization, the therapeutic effects are realized.

The drug can apparently circumvent the usual resistive facade of the alcoholic and get behind his defences and minimize them. The alcoholic, as a rule, cannot seem to accept the reality of his assets and has low self-esteem. The psychedelic experience may bring him to some reconciliation of his capabilities and liabilities. The individual sees clearly that some of his actions are not in line with his new knowledge and that changes are necessary. He sees his innate strengths and is able to evaluate them realistically.

The success of the programme is evaluated after an extensive follow-up, including a mailed questionnaire after 90 days and a personal interview 1 year after discharge. Ninety-five percent of the patients are available for follow-up. The following criteria are used to assess changes in life style and behavioural patterns.

1. abstinence from alcohol
2. attendance at Alcoholics Anonymous
3. regular employment
4. number of arrests
5. destructive aspects of drinking
6. time spent in hospital as result of drinking

This programme has resulted in 25% of the patients being abstinent at the end of one year[3]. This result is similar to that attained in published studies of other programmes. However it is felt that considering the other criteria, this programme seems to produce more desireable changes in the lives of patients. It is also worthy of note, that of 400 patients treated with LSD, there is no record of any detrimental side effects. Of these, only 3 "trips" have been terminated with thorazine because the patient remained at the psychotomimetic level.

I am still somewhat skeptical about the claims concerning LSD and its role in the treatment of chronic alcoholism. The important thing to remember is that evidence indicates that it does have some influence on changing the alcoholic's mode of life towards more acceptable social patterns. Its use in the right therapeutic setting can induce an experience which leads to some form of self-actualization. The event is profound and the drug seems to individualize, taking the patient's perception, distorting it and reintegrating it in a meaningful, positive direction. I feel that it is the responsibility of all medical people to keep an open mind concerning the drug. It is being used, apparently successfully, in the treatment of psychosomatic illness at certain research institutions. The need is too great and the present resources too inadequate for narrow-mindedness.

A. Connolly 6T8

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Medical Muses

Réné Théophile Hyacinthe Laennec (1781-1826)

Réné Théophile Hyacinthe Laennec (1781-1826), born in Quimper, Lower Brittany, lived in an age of history-shaping events exemplified by the French Revolution and Napoleonic Wars of his native France. Born of a doubly unsuccessful poet-lawyer father and reportedly consumptive mother, his embryonic genius could have languished but for an uncle, Guillaume Laennec, a distinguished physician in Nantes, with whom he went to live at seven years of age. Under this man's influence the young Réné developed a love of classic Latin prose and verse and at age ten translated the First Eclogue of Virgil into French verse. His uncle's persuasiveness turned Laennec from an interest in engineering to the profession of medicine, and at fourteen years of age he began his studies at the Hôtel Dieu. Coincident with his early medical training he learned Greek and perfected his knowledge of Latin which he used extensively in later life.

Laennec's diversified interests in music, art, the theatre, the flute, and poetry were hampered by the reluctance of his father to finance even his medical education. Many letters were sent from Nantes to Quimper, not unlike those of today's medical student.

> "My dear Father, I have no longer hat nor shirt nor a sou in my pocket; if you are as hard up as I am, I am sorry for you. If you are well off, I beg you to send me two louis."

After a period of frustration and delay, during which his fellow students had left the Hôtel Dieu for study in Paris, Laennec received a small amount of money. He made a ten day walk to Paris and enrolled in L'Ecole de Médecine under Corvisart, the founder of French clinical medicine, at the Charité. With Laennec's natural genius, his training in the classics and art, he was soon selected for the Society of Medical Instruction reserved for the élite of the students.

In 1802, at age twenty-one, Laennec published his first papers, the most important being a detailed study of six cases of peritonitis from bedside to autopsy room relating clinical and pathological findings. Until this time clinicians had confused peritonitis and enteritis, and his article won him immediate distinction. "He was practically the first internist to check his physical findings against pathological conditions as found at the post mortem many hundreds of times."

Laennec's early prominence was overshadowed by continuing poverty and ill health, and he sought consolation in his religion.

> Certainly its acceptance augmented that spirit of tolerance and kindliness that had always distinguished his character . . . And it was not uninfluential in the construction of his ideals . . . His only ambition was to make his life useful . . . and money, success and fame could, without that, yield no ultimate satisfaction.

At graduation the twenty-two year old Laennec won the Grand Prix in both Medicine and Surgery and followed his student successes by delivering an original course in Pathological Anatomy and writing for the Journal de Médecine.

In 1802 Laennec and his colleague Bayle (U. of T. Med. J., March 1966) had begun a study of tuberculosis by diligent autopsy investigation which enabled Laennec to deliver a famous lecture on the subject in 1804.

Laennec's eminence was gained at the expense of his health, and he suffered from asthma, angina, and chronic fatigue. He phrased his feelings in a manner fully unedrstood only by the ill when he wrote, "Health is a treasure recognized only after it has eluded us."

> But the manner was surprisingly energetic for so poor a physique, and though Laennec's demeanor was simple and modest, he radiated a consciousness of

power that inspired in his patients the utmost confidence . . . In the pursuit of the practice of medicine he was completely self-sacrificing; devoting himself to his patients, he surrounded them with countless attentions, and the fee was always the last thought.

During the years 1805 to 1811 Laennec's practice gradually increased to equal his academic stature but this was again offset by declining health.

A brilliant idea which led to the invention of the stethoscope help spread Laennec's fame beyond Europe. Finding it necessary to listen to the heart of a modest young woman, he rolled a piece of paper into a tube and found it conducted the sounds more clearly than ever before with ear to chest. Experimenting with instruments of varied material and form Laennec was able to undertake a detailed study of the clinical signs in chest pathology which culminated in "De l'Auscultation Médiate", in 1819. This two volume work embodied the terminology still used today to describe the auscultatory findings in the diseased chest.

Ironically, considering his important contributions to the progress of medicine, the name, "Laennec", is only associated today with the type of cirrhosis of the liver often found in the chronic alcoholic. Laennec devoted only the space of a footnote to its description in his "Mediate Auscultation" in a case of "chronic left-sided pleurisy with ascites and organic disease of the liver."

> "Cette espèce de production est encore du nombre de celles que l'on confond sous le nom de squirrhe. Je crois devoir la désigner sous le nom de cirrhose, à cause de sa couleur. Son développement dans le foie est une des causes les plus communes de l'ascite, et à cela de particulier qu'à mesure que les cirrhoses se développent, le tissu de foie est absorbé: qu'il finit souvent, comme chez ce sujet, par disparaître entièrement; et que, dans tous les cas, un foie qui contient des cirrhoses, perd de son volume au lieu de s'accroître d'autant. Cette espèce de production se développe aussi dans d'autre organes, et finit par se ramollir comme toute les productions morbifiques."

In 1819 Laennec suffered a severe nervous breakdown. After recouperating at a modest family estate which had passed into his hands, he returned to Paris in 1821 to accept the accolades deserved for the originator of auscultation.

During the following years, intensive work on the second edition of "Mediate Auscultation" combined with litigation over land in which he had lost 16,000 francs led to further illness and nervous breakdown in 1826. At this time, he developed the symptoms and signs of tuberculosis, the diagnosis of which was made easier by the use of the stethoscope. He hoped a return to his favoured Brittany would effect a cure, but his health progressively failed. Towards the end fever and delirium set in, but on the afternoon of his death a lucid interval prevailed.

> On August 13, 1826, he was in bed; at 3 p.m. he woke from his torpid state. His wife saw him take the rings off his fingers and place them on a table. She asked why he did this; he replied that it would soon be necessary that another should do this for him and that he did not wish that anyone should have the trouble. Two hours later, at the Place of the Foxes, the soul of one of the greatest of physicians left its body.

We, as future physicians in a society plagued with desires for economic success, should consider both the unselfishness of Laennec's contributions to medicine and his moral principles.

> "I shall consider it ample, yea more than sufficient reward for my labour, if it should prove the means by which a single human being is snatched from an untimely death."

B. N. French, B.Sc. 6T8

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Clinicopathological Conference

A. Gordon 6T8

JOINT CLINICOPATHOLOGICAL CONFERENCE, PRINCESS MARGARET - WELLESLEY HOSPITAL, (June 8, 1966)

"Unusual Complications of Multiple Myeloma"

HISTORY: *Dr. J. Lundon, Assistant Resident in Medicine, P.M.H.*

RADIOLOGY: *Dr. J. Davidson, Dept. of Radiology, P.M.H.-Wellesley*

PATHOLOGY: *Dr. J. S. Carruthers, Dept. of Pathology, P.M.H.-Wellesley*

DISCUSSION: *Dr. D. Bergsagel, Chief of the Dept. of Medicine, P.M.H.*

PHOTOGRAPHS: *courtesy of Photography Dept., P.M.H.*

DR. LUNDON:

A fifty-five year old lady was admitted to Saint Michael's Hospital with a two-year history of progressive and relentless weight loss. The precipitating feature which brought her into the hospital was massive enlargement of her tongue which interfered with her speaking and eating. A claudicative pain in her limbs became sufficiently severe to interfere with such activity as combing her hair. She also had exertional dyspnoea.

When she presented at Saint Michael's Hospital, the significant physical findings included cachexia, and loss of bulk in the muscles about her face and neck. Her tongue was grossly enlarged, yellow red, with atrophic papillae. There was bilateral enlargement beneath the rami of the mandibles, perhaps due to an increase in size of her submandibular glands, but more likely due to enlargement of the root of her tongue displacing the glands. She was anemic, and sternal marrow aspiration showed total replacement, by plasma cells, of the marrow. Her urine contained 4^+ protein, including Bence-Jones protein. Her BUN was 490 mgm %.

She was admitted to the Princess Margaret Hospital one month later. X-ray displayed apparently asymptomatic, disturbed, intestinal motility. She had no complaints relative to her intestine and her skeletal series showed only osteoporosis. Skeletal muscle biopsy taken at Saint Michael's Hospital and reviewed here indicated amyloid deposits between the muscle fibres and also within the walls of the arterioles and venules. Important physical findings included clubbing of the fingers, hypertrophy of calf muscles, and some degree of weakness in the hip.

An electrophoretic strip of serum protein revealed a total portein of 6.5 gm %; albumin was 3.87 gm %, alpha-1 globulins 0.23 mgm %, alpha-2 globulins 0.93 gm %, beta globulins 0.85 gm %, and gamma globulins 0.62 gm %. On the immunophoresis G immunoglobulins were normal and A immunoglobulins were markedly reduced. Because of a lack of antiserum, M immunoglobulins were not tested. Also found was a single protein which reacted with lambda antiserum. Kappa globulins were not found. Several urinalyses were performed during which the albumin fluctuated from 14.89 gms in twenty-four hours on admission, to 8.29 gms on the thirteenth hospital day. On the immunophoresis of the urine, lambda protein was also seen. Again there was no kappa protein.

Her therapy at the hospital consisted of Melphalan. On the third hospital day, 1 mg Melphalan was given per kilogram body weight. This amounted to 54 kg.

On the nineteenth hospital day, her platelets were 50,000 cu. mm. and Hgb was 8.8 gm%. Representative values for blood calcium, urea, and alkaline phosphatase were 10.3 mgm%, 77 mgm%, and 13.1 KA units respectively.

Her course was complicated by an episode of rectal bleeding which began in the fourteenth hospital day. The bleeding persisted and she received 1500 ml. of blood over three days. In spite of this, on the twenty-second hospital day, her blood pressure was 80/60 with a pulse rate of 140. She was in shock, being cold and sweaty. Her heart sounds were loud with multiple extrasystoles. Terminally she developed ileus and died on the twenty-fourth day.

DR. DAVIDSON:

The first radiological examination which this lady had was a complete skeletal survey. While this showed no evidence of myelomatosis, it did display generalized osteoporosis. The incidental findings may perhaps be of some interest:

She has fusiform periatricular swelling around her interphalangeal joints and terminal phalanges. There are

Fig. 1: X-Ray of Cervical Vertebra
The vertebra shows signs of degeneration and osteoporosis. A large soft shadow representing the tongue has decreased the A-P diameter of the pharynx.

Fig. 2: Plain Film of Chest
The cardiomegaly here is characteristic of amyloidosis.

also some peculiar erosions, the most common cause of which is uric acid deposition in soft tissue, but which are also described in amyloid disease. The deposition of amyloid in the periarticular areas may account for her soft tissue increase. The X-ray of her cervical spine shows that in addition to her evidence of disc degeneration and osteophytosis, she has a soft tissue plaque lying between her oesophagus and larynx: this would be a characteristic finding in an amyloid deposit. In the X-ray of the skull the interesting finding is the size of this lady's pharynx. The space between the tongue and palate is probably 2 mm., indicative of the gross macroglossia this lady had.

A barium meal film shows epithelial ridges with a thick wall. The duodenal mucosa is coarsened, and the pattern within the bowel is irregular in comparison with the normal jejunal pattern. The film of the barium enema suggests that the colon was rigid with an unusually thick wall. The mesentery might also be thickened. Either a thickened diaphragm, or a thickened colonic wall, or both, are seen in the chest film. The lung fields were clear and the heart was within normal size for the age of the patient. Another film was taken of the abdomen, ten days after the initial films, without the addition of any barium. Since it would be unusual to see this much barium in the large bowel ten days after a contrast dye has been used, I would take this as evidence of a decreased motility of the small bowel and colon. Once again this pattern of thickening of the mesentery, dilatation of the colon, and thickening of both the diaphragm and probably the wall of the colon is present.

Films taken of this lady when she was acutely ill show large fluid levels within the dilated loops of bowel. At this time we interpreted it as a large bowel obstruction. There is not a great deal of change in the lumen between this and the last examination, but in the latter there certainly is fluid. In retrospect, this must be blood, but one certainly cannot say this without knowing the clinical findings.

I would like to summarize the radiological findings possible in amyloid disease:

1. *Heart*—Cardiomegaly is present. This is very frequently confused with pericardial effusion because it gives the same diminution in the cardiac pulsation.

2. *Lung*—A nodular infiltration is seen, not unlike sarcoidosis. A localized lesion is often confused with both primary and secondary neoplasms. The amyloid deposition gives an increase in the bronchovascular markings both in the vessels and peribronchial tissues.

3. *Alimentary tract*—Macroglossia and localized deposits of the upper respiratory tract, as seen in this patient, may be found. Often plaques are discovered on contrast studies of the hypopharynx.

The esophagus is classically described as being tube-like with reflux and is confused with scleroderma. Secondary changes in the mucosa may sometimes be caused by the reflux.

The stomach shows a rigid type of gastric atrophy. A diagnosis of infiltrating scirrhous carcinoma may be made. The chronic gastric ulceration associated with amyloid is well described.

In the small bowel, there is a loss of motility from the diffuse and generalized amyloid deposition in the muscle coat. Also seen is a coarsened or irregular mucosal pattern.

The colon classically shows the atrophy and thick wall seen in this patient. Loss of motility is an important sign. One might differentiate this from ulcerative colitis because in colitis we see a contracted colon. Here we have a dilated, rigid colon. The mucosal alterations, however, are undifferentiable from colitis.

4. *Liver*—Hepatomegaly.

5. *Spleen*—Splenomegaly.

6. *Mesentery*—The mesentery becomes more prominent than on the normal film of the abdomen.

7. *Muscle*—Thickening of muscle is seen, such as macroglossia, and diaphragmatic thickening.

8. *Bones and Joints*—Deposition in bones and joints gives periarticular thickening of soft tissue, and marginal erosion. This patient showed both of these. As I previously mentioned, gout may be confused with this. The phalanges develop a lattice pattern which is confused with sarcoidosis.

9. *Endocrine*—Dystrophic calcification may be present in any lesion. Pancreatic calcification is frequently described.

10. *Lymph nodes*—Dystrophic calcification in seen here in 40% of cases. Unusual lymphangiographic patterns may be seen.

11. *Kidneys*—These patients with myelomatosis should not have an I.V.P. The I.V.P. has been known to cause protein deposition in tubules followed by renal failure.

DR. CARRUTHERS:

Up to now, we have dealt with the clinical and radiological picture of this patient. Now I would like to tell you what we found at autopsy. The diagnosis of multiple myeloma and amyloidosis was made at Saint Michael's Hospital. While protein and marrow studies are not available, we do have tissue biopsies. The gastrocnemius muscle was used. Microscopically dark, red striated muscle fibres are seen, widely separated by a rather pale, pink-staining material. This material stains metachromatically with cresyl violet, and has an affinity for congo red. What we are looking at is a number of vascular, blood-filled spaces. Much of the amyloid is in blood vessel walls producing great thickening of them. Of course, there is also deposition in the adventitial connective tissue. The second biopsy was taken from the rectum. The significant finding is a large, thick-walled blood vessel in the submucosa, probably an artery. A tongue biopsy show that the striated muscle fibres are very widely separated by a pale, pink-staining material which is amyloid. Much of this would just appear to be amyloid in the connective tissue.

At autopsy, this patient's vertebral bone marrow was rather pale and spongy. No focal lesions were detected; if there was anything there, it was diffuse. There is microscopic evidence of plasma cell infiltrations in the vertebrae, ribs and ilium. From a gross point of view, the gastro-intestinal tract was the most impressive part of the autopsy. The tongue was considerably involved, firm, and had a granular reddish color on the surface. Essentially, the microscopic picture is the same as seen

Fig. 3: Rectum (orig. magnification X125)
The wall of an arteriole in the submucosa is greatly thickened by amyloid.

at the biopsy, except that there are fewer muscle fibres. Coming down the G.I. Tract, the wall of the lower one-third of the esophagus was thickened up to almost 1 cm., and quite firm and rigid. We thought grossly the stomach and small intestine were normal, but that the colon was very striking. It was full of what we estimated to be 1000 cc. of fresh blood. The surface was rather blackened and ragged. The cross-section was very thick. While some mucosal folds were intact, there was extensive ulceration. Microscopically, there is no more mucosa evident. What remains is a massive deposition of amyloid. The sort of rounded structures seen are probably blood vessels greatly thickened by amyloid.

During the course of her illness, this lady had thrombocytopenia, and hypoprothrombinemia. These undoubtedly contributed to her gastro-intestinal bleeding. Another possibility would be a toxic or ulcerogenic effect upon the colonic mucosa of the agents with which she was treated. However, the tremendous amyloid thickening of the colon with deposition in vascular channels to the point where some vascular channels are narrowed, might well be sufficient to produce mucosal ischemia, ulceration, and hemorrhage. In this patient,

Fig. 4: Tongue (original magnification X40)
Striated muscle fibres (at bottom) are widely separated by homogeneous material. Large aggregates of similar material also produce a large subepithelial mass. This material has a special affiuity for Congo Red indicating its amyloid nature.

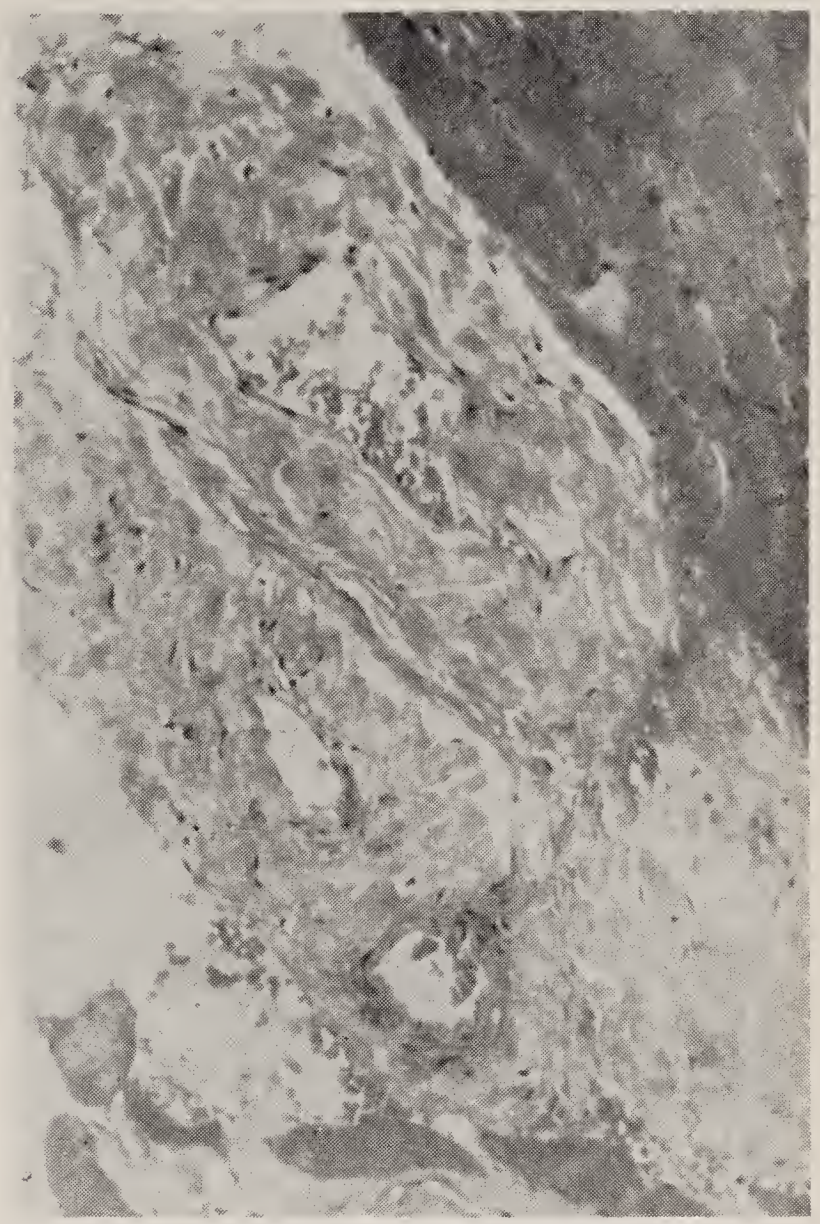

Fig. 5: Skeletal Muscle (orig. magnification X125)
In the connective tissue between muscle bundles are small vascular channels whose walls are greatly thickened by amyloid.

the massive gastro-intestinal bleeding was the immediate cause of death.

The heart weighed 355 gm. so that it was not enlarged, but there was a pearly thickening of the intima lining both auricles. This was shown to be a subendocardial amyloid plaque-like deposit measuring up to 3 cm. in thickness. Amyloid was present in vessel walls in both auricles and ventricles. The calf muscles were grossly hypertophied and pale, with the microscopic pattern of the original biopsy. In reference to Dr. Davidson's speculation concerning the diaphragm, it was quite thickened.

Amyloid was present in lesser amounts in other parts of the body. In all these areas the amyloid was present in blood vessel walls but there was no gross bulky or tumour-like accumulations. Amyloid was not identified in the kidneys. Instead this lady had what we would call a myeloma kidney or a myelonephropathy of a rather mild degree. She had casts of presumably Bence-Jones proteins filling a moderate number of collecting tubules with evidence of epithelial degeneration about them. I would think this renal change together with the gastro-intestinal hemorrhage probably contributed to the degree of terminal azotemia with which this lady presented. These were the pathological findings at autopsy. Do you have any questions at this point?

QUESTION:

Was her limb pain caused by vascular ischemia?

DR. CARRUTHERS:

Usually limb pain in primary or secondary amyloidosis is due to amyloid infiltration of the perineurium of the peripheral nerves. As we did not sample these in this patient, I cannot answer that question.

QUESTION:

Were the lymph nodes involved?

DR. CARRUTHERS:

They were grossly normal. Before turning the discussion over to Dr. Bergsagel, I would like to make a couple of points about the deposition of amyloid in this

patient. Amyloid is found in about 10% of patients with multiple myeloma. The main sites of deposition are usually those we think of as associated with primary amyloidosis, that is, in muscle be it cardiac, striated or smooth, the gastro-intestinal tract and blood vessel walls. When you mention primary amyloidosis it brings up the point that a number of studies have been done which demonstrate abnormal plasma cells, or abnormal numbers of plasma cells in the bone marrow of a great number of patients with primary amyloidosis. This condition and multiple myeloma may be more closely related than apparent at first glance. In secondary amyloidosis, by contrast, amyloid deposits are found typically in liver, spleen, kidneys and adrenals. These deposits are often masses interfering with the functioning of these organs. When these latter organs are involved in primary amyloidosis, or amyloidosis associated with multiple myeloma, the amyloid is very often just in blood vessel walls. In the liver of this patient, for instance, amyloid is found only in the hepatic arteries in portal tracts, so this does not produce enlargement or malfunction of the organ as a rule.

Dr. Davidson mentioned scleroderma. It is interesting that when amyloidosis occurs in the esophagus and in the intestine in conjunction with skin and subcutaneous deposition, the total picture is highly suggestive of scleroderma. The thickening and indurations of the skin are quite similar.

At this point I would like to ask Dr. Bergsagel if he will carry on and afterwards we will have a general question period.

DR. BERGSAGEL:

Well I wanted to discuss this case from two points of view: firstly, with respect to the pathogenesis of amyloidosis and secondly, the results of treatment of various types of plasma cell myeloma with Melphalan. Several lines of evidence suggest that a primary plasma cell dyscrasia is responsible for most cases of amyloidosis. First of all, in one autopsy series on well-defined cases of plasma cell myeloma, as long ago as 1931, Magnus Levi pointed out that 10% of autopsy cases show amyloidosis. This amyloidosis is especially common in patients who have Bence-Jones proteinuria as was evident in this case. The only abnormal protein found in this patient was the lambda type of Bence-Jones protein. Secondly, in a series of well-established cases of amyloidosis, an increased number of plasma cells and abnormal proteins can be found in a majority of patients. This was first pointed out by Apitz in 1940; the idea has since been developed to a greater degree by Osserman who reported the findings of 27 cases of amyloidosis. In 24 of these cases, the amyloid was distributed in the primary pattern as outlined by Dr. Carruthers, but in three of these cases the distribution of amyloid was of the secondary pattern. In all these cases, however, there was some evidence of a plasma cell dyscrasia. There is an increased number of plasma cells in the marrow of 26 of these cases, a reduced normal gamma globulin formation in 19, or an abnormal peak in the other 8. Twenty of these cases had a Bence-Jones protein in the urine. In 12 it was type K, and in 8, type L. In 4 cases the protein could not be typed, and in 3 cases there were no tests for Bence-Jones protein. The third line of evidence linking the Bence-Jones protein of myeloma with the development of amyloidosis, is the finding that the tissue binding affinity of Bence-Jones proteins from patients with amyloidosis is more marked than the binding of Bence-Jones protein from patients who do not develop myeloma. It is much more marked in the tissue binding affinity of amyloid or 7-S gamma globulin. These studies are done by binding a fluorescent dye such as fluorescein isothiocyanide to the Bence-Jones protein.

On the basis of these perhaps circumstantial findings Osserman has postulated that amyloid infiltrates represent insoluble aggregates or complexes of low molecular weight such as light polypeptide chains with tissue proteins and/or tissue polysaccharides. Other serum components such as fractions of the complement system may also participate in these complexes.

Despite this circumstantial evidence linking plasma cell dyscrasia to the development of amyloid, the exact pathogenesis and structure of amyloid is still uncertain. It is clear that these infiltrates contain both protein and polysaccharides but it is not clear which of these structures is essential to the formation of amyloid. Cohen and his co-workers in Boston have purified amyloid fibrils from patients by differential centrifugation and rendered these fibrils soluble in alkaline buffers. These fibrils are very interesting because when the pH is returned to 7, the fibrils reform in the buffer and show the characteristic birefringence that Dr. Carruthers has talked about. Now the protein in these purified fibrils does not contain any gamma globulin fractions. The protein is small and migrates in the region of albumen by immunoelectrophoresis. In addition, electron microscopy studies of purified amyloid fibrils have shown that the amyloid protein is very similar to the protein coat of certain viruses. Thus the structure and pathogenesis of amyloidosis is uncertain, but I think that there is some relationship of this disease to plasma cell dyscrasia.

Now I would like to talk about the response of patients with myeloma to Melphalan. Some years ago we found that the response of patients producing different types of myeloma protein was quite different. (See chart) That is, of the patients producing only Kappa Bence-Jones protein, all were objectively improved, whereas none of the patients that produced only Lambda Bence-Jones protein were benefitted. In the group that had an abnormal component in the serum, about half of the patients were improved. This difference in the response rate was also reflected in the survival in that

the patients producing type L Bence-Jones proteins had the shortest survival. The other two groups had the longer survival. Recently I brought these figures up-to-date for all of the type K and type L Bence-Jones protein producers that I have been able to find. In this Kappa group, 24 of the 28 cases were objectively improved by Melphalan therapy, whereas only 7 of the 23 type L have been benefitted. We have one of these cases here, and there was another case studied by the Southwest Cancer Chemotherapy Study Group. In patients producing G and A myeloma, it took anywhere from 25 to 150 days before the amount of protein in the serum fell to less than 50% of the original. The pattern of response in patients that produce type K Bence-Jones protein is very different in that they improve more rapidly. In all these cases the Bence-Jones protein had fallen to less than 50% of the original value within 3 weeks with a median of 8 days. Of the type L producing patients, we have only had one who has shown a continued and sustained decrease in the Bence-Jones protein. In the others there was either no drop or increase in the proteinuria, or else just a temporary drop.

In looking through the literature, I found one case report by John Bernard in Paris, in which he describes a patient with amyloidosis who was treated with Melphalan and in whom sustained improvement occurred. In this patient there was a reduction in the amount of amyloid deposits which could be palpated in the skin and observed in the tongue. This improvement took a long time before it could be demonstrated. I was surprised that improvement such as this would be observed because these deposits looked pretty permanent on the histological slides.

QUESTION:

Are all the cases with abnormal marrows considered to be myelomatosis?

DR. BERGSAGEL:

You can't tell the difference between normal and abnormal plasma cells with just a microscope. Osserman feels that all his cases had a plasma cell dyscrasia. Only thirteen of his twenty-seven cases had osteolytic lesions; however, he felt that the diagnosis of plasma cell dyscrasia could be substantiated by the association of marrow plasmacytosis, poor production of normal gamma globulin, and the presence of an abnormal protein in the urine and serum.

QUESTION:

I suppose that the diseases such as chronic TB, which are associated with secondary amyloid, are also associated with plasma cells in marrow.

DR. BERGSAGEL:

Yes, and often there is often only a single abnormal protein in the serum.

DR. BRUCE-ROBERTSON:

Is there a difference in urinary or renal damage as caused by the two proteins?

DR. BERGSAGEL:

None that I know of. Osserman has been unable to demonstrate any difference in tissue binding properties. I know of no difference between the frequency of myeloma kidney in these two types. It occurs in both.

QUESTION:

Is the plasma cell required or will the lymphocyte also produce this condition?

DR. BERGSAGEL:

Many people think they are just different stages in development of the same kind of cells. There is some evidence that the plasma cell differentiates from a stem cell which looks very much like a lymphocyte.

In most patients who develop amyloidosis, the predominant abnormal cell is the plasma cell, rather than the lymphocyte.

DR. CARRUTHERS:

If there are no other questions, I would like Dr. Bergsagel to sum up.

EFFECT OF MELPHALAN ON DIFFERENT PLASMA CELL TUMOURS

Melphalan Response:	Responders		Intermediate Response	Non responders (no objective response)
Myeloma Protein:	No Myeloma Protein	Type K Light Chain Protein	G- and A-Myeloma Proteins	Type L Light Chain Protein
Number objectively improved over number of evaluable cases	5/6	11/11	30/65	0/9
Survival from onset of symptoms: 1. Median Survival (months)	36+	68	55	23
2. 95% confidence interval (months)		43-109	45-67	18-31
Number Dead per Total number	0/6	4/12	25/70	6/9

DR. BERGSAGEL:

I can summarize it by saying that this is a classical case of amyloidosis complicating the course of a patient with plasma cell myeloma, and demonstrating that the most noxious feature of the disease was the abnormal protein. This patient did not die from destruction caused by proliferation of plasma cells in the marrow nor from anemia or the other features you associate with tumour. She died as a result of the formation of amyloid which is probably related to the type of protein she had been producing.

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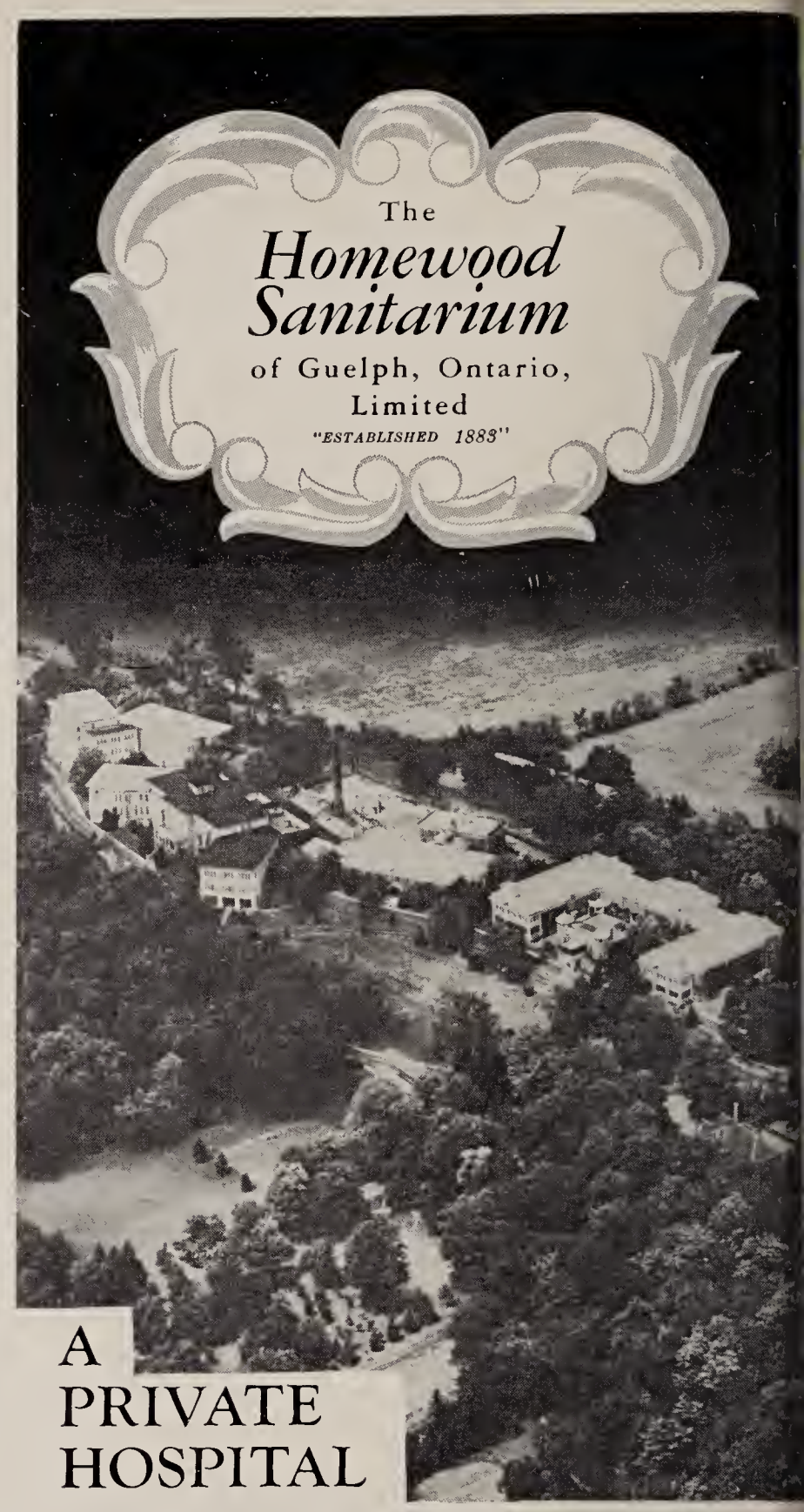

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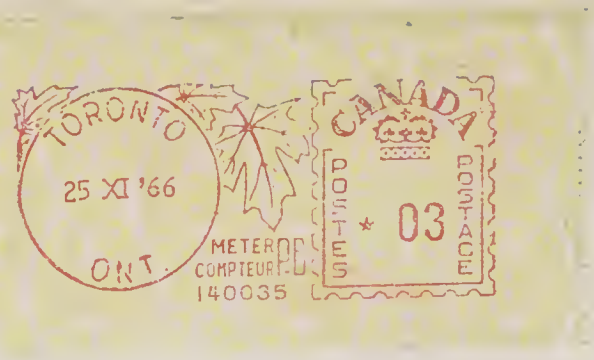

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